Remarks

No amendments have been made to the claims.

1. Rejection under 35 U.S.C. 103(a)

Claims 1 to 8 are rejected as allegedly obvious over EP 1024139 to Kizaki *et al.* ("Kizaki") in view of Am. Inst. Chem. Eng. J. (1984) 44(3): 612-646 to Naik *et al.* ("Naik"). The Examiner indicates that Applicant claims a process that employs a phosphonium phase transfer catalyst. According to the Examiner, Kizaki teaches a similar process that uses an ammonium phase transfer catalyst and Naik teaches that ammonium and phosphonium phase transfer catalysts are well known and commonly used. Therefore, the Examiner asserts that one of ordinary skill in the art would have known to substitute the ammonium phase transfer catalyst used in the Kizaki process with a phosphonium phase transfer catalyst to arrive at Applicant's claimed invention.

Applicants submit that Naik is a review article directed to phase transfer catalysts and methods of modeling phase transfer catalyst reactions. Several catalysts are listed, including ammonium and phosphonium phase transfer catalysts. Applicants point out that while Naik does teach that these catalysts find application in a range of industrial procedures, Naik does **not** teach that they may be used interchangeably in any specific process. On the contrary, Naik emphasizes a number of differences between ammonium and phosphonium phase transfer catalysts, including differences in their relative stabilities and activity characteristics (see, *e.g.*, Table 1 on page 615 of Naik). In fact, Naik makes it clear that the selection of a phase transfer catalyst for a particular objective is typically decided by using an empirical approach in which catalysts are screened to determine their suitability for that particular objective (see, *e.g.*, section on page 615 of Naik entitled "Choice of PT catalyst" and sentence bridging columns 1 and 2 on page 615). This teaching of an experimental approach to choosing a catalyst with the proper characteristics is reinforced by the statement made in Naik that "the exact choice of catalyst depends on the system under consideration" (top of column 1 on page 616 of Naik) and by the recommended screening procedure involving catalysts under consideration. Thus, Naik stands

for the teaching that while ammonium and phosphonium phase transfer catalysts may both be used in some systems, they clearly cannot be considered to be interchangeable in all systems. Accordingly, a person of ordinary skill in the art would not have an expectation of success from a reading of Naik of substituting an ammonium phase transfer catalyst with a phosphonium phase transfer catalyst.

The teaching of Kazaki is specifically for an ammonium phase transfer catalyst. A person of ordinary skill in the art would likely presume that the selection of such a catalyst was the result of a screening procedure and would not have been motivated to replace it with another class of catalyst as suggested by the Examiner. The Halpern article Phase Transfer Catalysis Communications (1997) 3: 1-12 (a copy of which is submitted for the Examiner's consideration) suggests simply choosing a phase transfer catalyst for a first experiment and then beginning a rational "decision tree" evaluation of other catalysts that are either, based on the obtained results, similar to or different from the first chosen catalyst. This approach is suggested only in the absence of available data that points to the use of a specific catalyst. Kazaki is an example of a reference that points to the use of a specific phase transfer catalyst because it clearly directs a person of ordinary skill in the art toward the use of tetra n-butylammonium halides as the choice for a phase transfer catalyst for esterification reactions (see, *e.g.*, Examples 7 and 8 of Kazaki).

The Halpern review article broadly supports the choice of ammonium-containing catalysts as a first choice for esterification reactions, which is the type of reaction recited in Applicant's claims. All of the catalysts listed in Halpern in connection with an esterification reaction are ammonium catalysts. Halpern discusses the variation between ammonium catalysts with different ligands (see, *e.g.*, the definitions of TBAB, Aliquat 336® and TEBAC given on page 1), but there is no teaching or suggestion of any catalyst other than an ammonium-containing catalyst for use in an esterification reaction. The results provided in Halpern clearly illustrate how simply varying the ligand(s) on a catalyst can have a dramatic effect on the result achieved. The effects resulting from a more fundamental change in the catalyst – namely, changing from an ammonium-based catalyst to a phosphonium-based catalyst – would be expected to have an even more dramatic effect, and so a person of ordinary skill in the art would

not be, as a matter of procedure, likely to consider this option. In fact, if one looks at other art in this area, it is apparent that, in relation to the reaction systems that are the subject of the subject application, the use of ammonium salts is commonly accepted.

Bram *et al.*, both in Tetrahedron Letters (1982) 23: 5407-5408 and Israel Journal of Chemistry (1985) 26: 291-298 (copies of which are submitted for the Examiner's consideration), discuss catalysis of alkylation reactions generally, and in all cases, the catalysts used are ammonium catalysts. That the clear preference in this art for using ammonium catalysts is further illustrated in the extract from Phase Transfer Catalysis, Principles and Techniques (C.M. Starks; Academic Press (1978)) in which carboxylate ion displacement reactions are summarized, and all successful reactions were carried out in the presence of ammonium-containing catalysts. On the few occasions were phosphonium catalysts were used, no ester product was found to be present (see (-) in "Yield %" column in Table 21).

Further, in U.S. Patent No. 5,594,153 (a copy of which is submitted for the Examiner's review), the reaction of step (d) can be viewed as analogous to the process claimed by Applicant in the subject application, and for this procedure, ammonium salts are the catalysts of choice (see, *e.g.*, column 6, lines 21 to 31; column 13, lines 56-60; column 15, line 16; column 16, line 62; and column 20, line 46). There is absolutely no teaching or suggestion that the reaction of step (d) should be conducted in the presence of phosphonium ions.

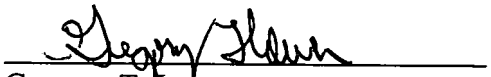
At least in view of all of the above-discussed evidence regarding the use of ammonium-containing salts as catalysts in the context of esterification/alkylation reactions, Applicant submits that a person of ordinary skill in the art would not consider replacing the ammonium-containing phase transfer catalyst of Kizaki as suggested by the Examiner. Clearly, the generalized and non-specific teaching of Naik would not be sufficient to provide the necessary degree of motivation to overcome the general understanding taught in the art. Accordingly, Applicant submits that the claims of the subject application should be acknowledged by the Examiner as nonobvious over the combination of Kazaki and Naik, resulting in the withdrawal of this rejection.

2. Conclusion

The foregoing remarks are intended to convince the Examiner of the patentability of the pending claims. A favorable action is awaited. Should the Examiner find that further discussion would be of value, the Examiner is invited to telephone the undersigned at his convenience.

EXCEPT for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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C.M. Starks, C.L. Liotta, "Phase Transfer Catalysis, principles and techniques" Academic Press, 1978

TABLE 19

Phase Transfer Catalyzed Reactions of Na_2S with Alkyl Halides to Yield Dialkyl Sulfides [74, 75]

Alkyl halide	Na_2S (mol eq)	Catalyst[a] (mol eq)	Temp. (°C)	Time (min)	Yield of sulfide (%)
$1\text{-}C_6H_{13}Cl$	0.6	0.1	70	40	99,[b] 90[c]
$1\text{-}C_8H_{17}Cl$	2.5	0.1	70	40	99,[b] 91[c]
	1.0	0.1	70	40	98[b]
	0.6	0.1	70	40	98[b]
	0.6	0.05	70	70	98[b]
	0.6	0.033	70	120	98[b]
	0.6	0.025	70	160	97[b]
$C_6H_5CH_2Cl$	0.6	0.1	70	10	100,[b] 94[c]
$n\text{-}C_6H_{13}CH(CH_3)Cl$	0.6	0.1	70	300	98,[b] 90[c]
	0.6	0.1	110	120	99[b]
$1\text{-}C_8H_{17}Br$	0.6	0.1	70	20	100,[b] 91[c]
	0.6	0.033	70	70	98[b]
$n\text{-}C_6H_{13}CH(CH_3)Br$	0.6	0.1	70	80	99,[b] 91[c]
$(CH_3)_3CCH_2Br$	0.6	0.1	70	500[d]	90,[b] 81[c]
$+CH_2-CH+_n$[e] $C_6H_4CH_2Cl$	7.0 (NaSH)	0.15[f]	100	24 hr	95[g]

[a] Hexadecyltributylphosphonium bromide as catalyst.
[b] GLC analysis.
[c] Isolated yield.
[d] Reaction carried out under N_2.
[e] Resin beads of lightly cross-linked poly(styrene–vinylbenzyl chloride). This run from Mitchell *et al.* [75].
[f] Catalyst was tetra-*n*-butylammonium bisulfate.
[g] Product was RSH rather than RSR.

TYPICAL PROCEDURE: *n-Octyl Sulfide* [74] Reprinted with permission from D. Landini and F. Rolla, *Synthesis*, p. 565 (1974). 1-Chlorooctane (14.9 g, 0.1 mol), sodium sulfide nonanhydrate (14.4 g, 0.06 mol), hexadecyltributylphosphonium bromide (5.1 g, 0.01 mol), and water (30 ml) were mixed in a flask equipped with magnetic stirrer and reflux condenser, and heated at 70° (bath temperature) with vigorous stirring. The reaction was followed by G. L. C. (SE 30, 3% over Chromosorb at 125°). After 40 min (99% conversion) the organic layer was separated, washed with water, dried over calcium chloride and vacuum distilled to give *n*-octyl sulfide, yield: 11.6 g (91%); b.p. 160–162°/4 torr; $n_D^{20} = 1.4690$ . . . .

By treating the distillation residue with light petroleum, 4.6 g (90%) of the phosphonium salt, m.p. 52–54°, were recovered. Small quantities of product and catalyst can be obtained by extracting the aqueous phase with ethyl ether.

V. Carboxylate Ion Displacements

It has long been known [76, 77] that aqueous solutions of sodium alkanoates react with alkyl halides in a second phase, provided an amine is

TABLE 20

Comparison of Various Quaternary Ammonium Halides as Phase Transfer Catalysts for the Reaction of 1-Chlorobutane with Sodium Benzoate[a]

Quaternary salt	Yield of butyl benzoate (%)
$(CH_3)_4N^+ Br^-$	Trace
$C_6H_5CH_2(CH_3)_3N^+ Cl^-$	5.3
$C_{12}H_{25}C_6H_4CH_2(CH_3)_3N^+ Cl^-$	56.7
$1\text{-}C_7H_{15}(CH_3)_3N^+ Br^-$	72.3
$1\text{-}C_7H_{15}(CH_3)_3N^+ I^-$	91.3

[a] From Hennis *et al.* [86]. Reaction conditions: 1.5 moles sodium benzoate, 1.5 moles 1-chlorobutane, and 0.0372 mole quaternary salt at 113°C for 2 hr.

added as catalyst. Although a number of workers [78–85] have examined this two-phase reaction system in detail and postulated mechanisms to account for the catalytic activity of the amine, it remained for Hennis and co-workers [86, 87], to demonstrate that quaternary salts were formed in situ and that these functioned as phase transfer catalysts (Reaction 37). The

$$R'_3N + RX \longrightarrow R'_3\overset{+}{N}R\ X^- \qquad (37)$$

$$\underset{\text{org}}{RX} + \underset{\text{aq}}{R'CO_2Na} \xrightarrow{Q^+} R'CO_2R + NaX$$

use of trialkylamines is particularly effective when benzyl chloride or other highly reactive RX is used, since these rapidly form quaternary salts. With quaternary salts as catalysts for the preparation of butyl benzoate, Hennis *et al.* [86] showed that the catalyst needs to have at least one moderately long alkyl group (Table 20) to function well. Benzyl-containing quaternary salts were rather ineffective for this reaction, presumably because of low thermal stability. Results for a number of carboxylate displacements are listed in Table 21 [61, 63, 77, 78, 86–98]

Cainelli and Manescalchi [99] have demonstrated that anion exchange resins may be used in a three-step procedure to prepare esters (Reaction 38).

$$\underset{\substack{\text{Amberlite IRA-904}\\ \text{macroreticular resin}}}{[\text{resin}]\text{-}N^+(CH_3)_3Cl^-} + NaOH \longrightarrow [\text{resin}]\text{-}N^+(CH_3)_3OH^- \qquad (38)$$

$$[\text{resin}]\text{-}N^+(CH_3)_3OH^- \xrightarrow{RCO_2H} [\text{resin}]\text{-}N^+(CH_3)_3X^- \xrightarrow{R'X} [\text{resin}]\text{-}N^+(CH_3)_3RCO_2^-$$

50–90% yields

This procedure, which corresponds to a resin-bound ion pair extraction technique, works best with alkyl iodides. Runs performed with catalytic

TABLE 21
Phase Transfer Catalyzed Ester Syntheses

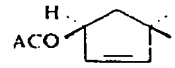
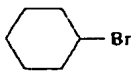
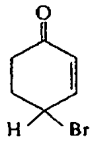
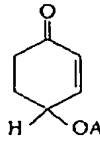
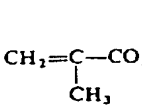
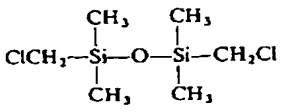
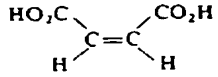
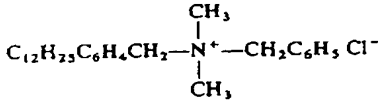
Acid	RX	Catalyst	Product (Yield, %)	Ref.
CH_3CO_2H	1-$C_5H_{11}Cl$	Et_3N	Ester (46)	63
	$(CH_3)_3CCl$	Et_3N	No reaction	61
		$(C_8H_{17})_3N^+C_3H_7Br$	 (75)	88
		Et_3N	 (66)	61
		$(C_8H_{17})_3N^+C_3H_7Br^-$	 (—)	88
	$C_6H_5CH_2Cl$	Et_3N, $(C_6H_5)_3P$, $(n\text{-}C_4H_9)_3N$, $(n\text{-}C_5H_{11})_3N$	Ester (93)	63
		Et_3N	Ester (75)	61
		Variety of crown ethers	Ester	8[illegible]
		Wide variety of amines	Ester (> 90)	87, 77
	1-$C_8H_{17}Br$	$(C_8H_{17})_3N^+C_3H_7Br^-$	Ester ( )	88
	Myrcene hydrochloride	Et_3N	Geranyl acetate (75–80)	89
		Et_3N	α-Terpinyl acetate (8–10)	90
		Et_3N	Linalyl acetate (8–10)	63
	Bornyl chloride	Et_3N	No reaction	89
	Pinocarvyl chloride	Et_3N	No reaction	89
	Carvyl chloride	Et_3N	Carvyl acetate (90)	89, 90
$CH_3CH_2CO_2H$	CH_3Cl	Et_3N	Ester (96)	87
	$CH_2{=}CHCH_2Cl$	Et_3N	Ester (87)	87
	1-C_4H_9Cl	Et_3N	Ester (80)	87
$CH_2{=}CHCO_2H$		Quaternary phosphonium salts	Ester (—)	91
	$C_6H_5CO_2CH_2CH_2Cl$	$C_6H_5CH_2N^+Me_3Cl^-$	Ester (77)	9[illegible]
	$p\text{-}C_6H_4CO_2CH_2CH_2Cl$	$C_6H_5CH_2N^+Et_3Cl^-$	Ester (—)	92
	$C_6H_5CO_2(CH_2)_4Cl$	$C_6H_5CH_2N^+Et_3Cl^-$	Ester (—)	92
$CH_3CH_2CH_2CO_2H$	CH_2Cl_2	$(C_4H_9)_4N^+HSO_4^-$	$(RCO_2)_2CH_2$ (79)	93
		$(CH_3)_4N^+Cl^-$	Ester (91.3)	94
		Phosphonium salts	Ester (—)	91
		Et_3N	Diester (45)	61
$HO_2C(CH_2)_2CO_2H$	CH_2Cl_2	$(C_4H_9)_4N^+HSO_4^-$	No reaction	93
	1-$C_{10}H_{21}$—Cl	Et_3N	Diester (74)	78
$(CH_3)_3CCO_2H$	CH_2Cl_2	$(C_4H_9)_4N^+HSO_4^-$	$(RCO_2)_2CH_2$ (80)	93
$HO_2C(CH_2)_4CO_2H$			Resin	95

TABLE 21 (continued)

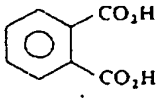
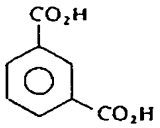
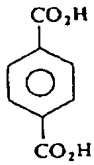
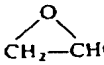
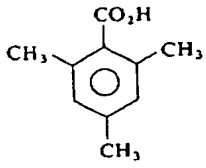
Acid	RX	Catalyst	Product (Yield, %)	Ref.
$C_6H_5CO_2H$	CH_3Cl	Et_3N	Ester (96)	87
	CH_2Cl_2	$(C_4H_9)_4N^+HSO_4^-$	$(RCO_2)_2CH_2$ (88)	93
	1-C_3H_7Cl	Et_2S or $(C_6H_5)_3P$	Ester (—)	96
	2-C_3H_7Cl	Et_2S or $(C_6H_5)_3P$	Ester (—)	96
	CH_2=$CHCH_2Cl$	Et_3N	Ester (93)	87
		Et_2S or $(C_6H_5)_3P$	Ester (—)	96, 86
	1-C_4H_9Cl	Et_3N	Ester (85)	87
	$(CH_3)_3C$—Br	Et_3N	Ester (12)	78
	1-$C_6H_{13}Cl$	Et_3N	Ester (47)	61
	$C_6H_5CH_2Cl$	Et_3N	Ester (79)	61
			(89)	87
p-$ClC_6H_4CO_2H$	CH_2Cl_2	$(C_4H_9)_4N^+$ HSO_4^-	Ester (84)	93
p-$O_2NC_6H_4CO_2H$	CH_2Cl_2	$(C_4H_9)_4N^+$ HSO_4^-	Ester (85)	93
o-$HOC_6H_4CO_2H$	CH_3Cl	Et_3N	Ester (98)	87
	CH_2=$CHCH_2Cl$	Et_3N	Ester (87)	87
	1-C_4H_9Cl	Et_3N	Ester (92)	87
	CH_2Cl_2	$(C_4H_9)_4N^+$ HSO_4^-	No reaction	93
		$C_6H_5CH_2N^+Me_3$ Cl^-	Diester (—)	97
			Resin (—)	95
	1-$C_8H_{17}Cl$	Et_3N	Ester (98)	78
	1-$C_{10}H_{21}Cl$	Et_3N	Ester (87)	78
	CH_2Cl_2	$(C_4H_9)_4N^+$ HSO_4^-	Polymer	93
$CH_3(CH_2)_7CO_2H$		$C_6H_5CH_2N^+Me_3$ Cl^-	Ester (—)	97, 98
$HO_2C(CH_2)_7CO_2H$		$C_6H_5CH_2N^+Me_3$ Cl^-	Diester (—)	97, 98
p-$CH_3COC_6H_4CO_2H$	CH_2Cl_2	$(C_4H_9)_4N^+$ HSO_4^-	$(RCO_2)_2CH_2$ (85)	93
$CH_3(CH_2)_8CO_2H$	1-$C_{12}H_{25}Cl$	Et_3N	Ester (82)	78
$HO_2C(CH_2)_8CO_2H$		$C_6H_5CH_2NMe_3^+$ Cl^-	Diester (—)	97, 98
	CH_2Cl_2	$(C_4H_9)_4N^+$ HSO_4^-	$(RCO_2)_2CH_2$ (87)	78

TABLE 21 (*continued*)

Acid	RX	Catalyst	Product (Yield, %)	Ref.
	CH_2Cl_2	Et_3N	$(RCO_2)_2CH_2$	78
	$ClCH_2CH_2Cl$	Et_3N	(91)	78
	1-C_4H_9Cl	Et_3N	(90)	78
	1-$C_8H_{17}Cl$	Et_3N	(84)	78
	2-$C_8H_{17}Cl$	Et_3N	(89)	
Ampenicillin	Alkylating agents	Quaternary salts or crown ethers	Penicillin esters	98a
$CH_3(CH_2)_{16}CO_2H$		$C_6H_5CH_2N^+(CH_3)_3\ Cl^-$	Ester (—)	98

amounts of resin did not give satisfactory results. Starks [16], using the general procedure described next, obtained 95–98% yields of a variety of esters from simple alkyl halides and sodium carboxylates.

PREPARATION: *1-Decyl Acetate* [16] A mixture of 55 g (0.25 mole) of 1-bromodecane, 270 g (2.0 moles) of sodium acetate trihydrate, and 10 g of $(C_{10}H_{21})CH_3N^+Cl^-$ was heated to 105°C with good stirring for 1 h. Water (350 ml) was added. The organic layer was separated and dried over anhydrous Na_2SO_4. 1-Decyl acetate in 97% yield was recovered from the quaternary salt catalyst by distillation through a wiped-film, short-path evaporator at 100°C and 0.1 Torr.

The water of hydration in $NaOAc{:}3H_2O$ is sufficient to form a liquid aqueous phase at 105°C so no water was added in this run. The large excess of sodium acetate used is necessary to overcome the unfavorable preference of quaternary cation for bromide over acetate ($K_p \simeq 0.05$ AcO^-/Br^-). Greater efficiency in acetate use can be realized by using a lower sodium acetate: alkyl halide mole ratio (~1:1) with three or four replacement steps of the aqueous phase by fresh sodium acetate. With larger carboxylate ions (propionate, butyrate, pentanoate, etc.) the anion partitioning ratio becomes increasingly more favorable, so that with acids larger than hexanoic, only one step with about 2 moles of sodium alkanoate per mole of alkyl halide is required for essentially complete conversion.

Brändström [3] has demonstrated that high yields (>90%) of esters may similarly be obtained by the ion pair extraction technique. This technique may also be used to prepare methylene esters in 60–to 90% yields from carboxylic acids and dichloromethane (Reaction 39).

$$CH_2Cl_2 + (C_4H_9)_4N^+\ RCO_2^- \longrightarrow (RCO_2)_2CH_2 + (C_4H_9)_4N^+\ Cl^- \qquad (39)$$

The poor nucleophilicity of acetate ion toward various substrates in condensed systems has been attributed to a combination of polarizability, basicity, and solvation factors. Liotta *et al.* [29] reported that acetate solubilized as the potassium salt in acetonitrile or benzene containing 18-crown-6 became sufficiently nucleophilic to react smoothly and quantitatively, even at room temperature, with a wide variety of organic substrates under LS-PTC conditions. Displacement reactions at 1°, 2°, 3°, and benzylic positions, along with competing elimination processes, have been demonstrated with this reagent, which has been termed "bare" acetate. The data summarized in Table 22 [100] deal specifically with the solvent acetonitrile. The same products were obtained in benzene but the reaction rates were slower. In the absence of crown, little or no reaction took place under identical conditions covering the same periods of time. For instance, in the case of benzyl bromide (run 1, Table 22), the most reactive substrate reported in Table 22, less than 5% benzyl acetate was formed after several days with

Anionic Activation by Solid–Liquid Phase Transfer Catalysis Without Solvent: An Improvement in Organic Synthesis

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(Received 26 February 1984)

Nowadays, and more than ever, organic synthesis involves economical (cost of materials, solvents and energy) and environmental (toxicity, pollution) problems. Therefore, performing organic reactions without solvent, efficiently and economically, is of interest.

The aims of this article are:

(a) to emphasize the possibility of performing many organic reactions, dealing with anionic activation, *in the absence of organic solvent;*

(b) to advocate solid–liquid phase transfer catalysis (PTC) without solvent;

(c) to indicate that many reactions can be carried out without solvents under very mild conditions and with an easy work-up, giving high yields at comparatively low temperatures (very often at room temperature); in some cases in competitive reactions, performed under these conditions, selectivity is observed.

In this paper, we shall compare our results with those obtained using other methods for anionic activation. It is known that an efficient anionic activation is obtained when the nucleophilic anion N^- is not solvated, and when the ion pair N^-M^+ is effectively dissociated. This is achieved by the use of homogeneous reactions in polar aprotic solvents (expensive, often toxic and difficult to remove); by classical PTC methods [1–4], i.e., generally in the presence of organic solvents such as benzene, toluene, methylene chloride chloroform, etc.; anionic activation reactions can also be conducted with supported reagents on mineral solids (alumina, silica clays, etc.).

We became interested in mineral support utilization for anionic activation through the work of E. Keinan and Y. Mazur [5] (1977), which deals with the oxidation of a nitro group into carbonyl (Nef reaction) on "basic" silica gel. This work showed that nitro compound absorbed on the solid support, in the absence of organic solvent ("dry media"), generates a nitronate anion which leads to a carbonyl group. Mazur and co-workers extended this methodology to other types of reactions performed on silica, including oxidation with oxygen atoms [6a], ozone [6b], or $FeCl_3$ [6c].

Since 1979, we have undertaken a systematic study of anionic activation reactions on solid inorganic supports (carboxylates, cyanide, fluoride, etc.). Alkaline salts of stable anions are directly impregnated on the support (alumina being the more effective), while salts of non-stable anions are generated in situ on support by reacting a base with the conjugated acid of the anion (malonate, acetoacetate, phenoxides, etc.). The alkylations of these supported anionic species are very efficient and involve milder reaction conditions, simpler work-up and higher selectivity than when run in organic solvents. We have also reported [8] the reduction of carbonyl and α,β-unsaturated carbonyl compounds by $M^+BH_4^-$ (M^+ = Li^+, Na^+, K^+, $\overset{+}{N}Bu_4$) on solid inorganic supports in "dry media" conditions; we observed that the reaction rate decreases when a solvent (diethyl ether) was added, without any change in the selectivity (1-2 versus 1-4 reduction for α,β-unsaturated ketones). The selectivity is different from that observed in an etheral solution, and this fact is indicative that reaction occurs on the support, even when a solvent is present.

As already pointed out, alumina was the most effective support for alkylation, but the yield of the alkylation of $CH_3CO_2^-K^+$ by $nC_8H_{17}Br$ on silica gel could be significantly improved by adding small amounts of a quaternary ammonium salt (NBu_4HSO_4, or, much better, $C_{16}H_{33}N(CH_3)_3Br$) to the support. When a quaternary ammonium grafted silica (Spherosil QMA, Rhone–Poulenc) is used as the support, a dramatic increase of the reaction rate is observed. We proposed an interpretation based on the nature of the superficial charge of the solid, however, cation exchange may also be considered.

We then undertook a systematic study of the nature and of the amount of the mineral support. It appears that solid $CH_3CO_2^-K^+$, finely ground, reacts with an equimolecular quantity of alkylating agent in the presence of a catalytic amount of tetrakyl ammonium salt. *Neither solvent nor support are necessary for the reaction*. Yields thus obtained compared favourably with those derived from the use of alumina as support or with those obtained by other methods recently described. The reaction conditions are very mild (often room temperature) and the work-up is simple: after vigorous stirring for 10 min with a mechanical stirrer, the mixtures are left aside at the appropriate temperature. After reaction completion, organic products are eluted by simple filtration on Florisil (on which ammonium salts remain adsorbed) with diethyl ether or dichloromethane. Proof

Table 1. Synthesis of Alkyl Acetates of Alkylation of Acetate Anion: Comparison of Recent Methods

Method \ Ester	$AcOCH_2-CH=CH_2$		$AcO_nC_nH_9$		$AcO_nC_8H_{17}$		$AcOCH_2Ph$		$AcOnC_{16}H_{33}$	
Our results [10]	2h	RT[a] 98%	10h RT	93%	20h RT	98%	2h	RT 99%	30h RT	92%
			2h 60°C	98%	2h 60°C	98%			3h 75°C	98%
Reactions on alumina without solvent ("dry media")			20h 85°C	50% [7b]	5h 85°C	95%			20h 85°C	88%
Reactions on alumina in presence of toluene or benzene					91h 90°C	66% [20]				
					100h 90°C	89% [21]				
Solid–liquid CTP					3h 83°C	96% [22]	2h	25°C 100% [22]		
Liquid–liquid CTP	46h	25°C 90%					0.25h	25°C 90% [23]		
Gas–liquid CTP								150°C 100% [24] (20 mm Hg)		
PEG 400 grafted silica + toluene			3h	110°C 56% [25]						

a. RT = room temperature.

that we are clearly dealing with *solid–liquid* PTC, without added solvent, is the fact that no reactions take place in the absence of ammonium salt.

We will now describe some results obtained by extending this approach to anionic reactions, mainly alkylations.

I. ESTER SYNTHESIS

$$\underset{\text{solid}}{CH_3CO_2^-M^+} + \underset{\text{liquid}}{R'X} \xrightarrow{NR''_4X} \underset{\text{liquid}}{RCO_2R'} + \underset{\text{solid}}{M^+X^-}$$

(a) Acetate Alkylation [10]

Alkyl acetates are obtained in very good yields. Two quaternary ammonium salts were examined as catalysts, NBu_4Br and Aliquat 336; the latter compound, which consists essentially of $(C_8H_{17})_3NCH_3Cl$ [11], is known as one of the most efficient PTC catalysts in liquid–liquid [12] and in solid–solid [13] conditions.

Aliquat 336 is far superior to NBu_4Br for acetate alkylation performed with nC_4H_9Br, $nC_8H_{17}Br$ and $nC_{16}H_{33}Br$: *alkyl acetates are thus obtained with yields >92% at room temperature.* For the reactions involving $PhCH_2Br$ and $Br(CH_2)_3Cl$, or $CH_2=CH-CH_2-Br$, the relative efficiency of NBu_4Br and aliquat is the same (NBu_4Br being slightly superior to aliquat). In both cases, a quasiquantitative yield is obtained at room temperature. Using $Br(CH_2)_3Cl$ as a reagent, Br is specifically displaced by the acetate anion. In alkylations with n-octyl halides, leaving group sequence Br > Cl > I was observed, similar to that of some PTC reactions, and different from that previously observed in homogeneous reactions [11,14].

Two explanations can be proposed for this effect:

(i) A lower solubility of CH_3CO_2-NR_4^+ in alkyl iodides

(ii) A solubility of the ammonium iodide which is formed in the reaction, and thus an inhibition of the PTC process, as previously proposed [14,15].

Only a few examples of solid–liquid PTC without added solvent [16–19] can be found in the literature. In 1967, H.E. Hennis described the synthesis [16] of some alkyl carboxylates, the catalysts being tertiary amines or quaternary ammonium salts. However, higher temperatures were needed with Hennis's method than with ours to obtain good yields. For example, to reach 98% of benzyl acetate, 2h at 125°C was required with Hennis' method, and only 2h at room temperature with ours to obtain 99% of this product.

Table 1 shows the best results obtained by us, compared with those obtained by utilization of other recent methods of anionic activation leading to alkylacetate synthesis. Formiate anion alkylation, leading to alkyl formates, are under current investigation by Y. Sasson and H.A. Zahalka [26].

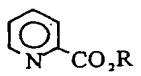
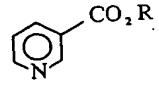
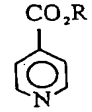
(b) Aromatic Carboxylates Alkylation [27]

Alkyl esters can also be prepared from aromatic carboxylates, and good yields are obtained under very mild conditions, which compare favourably with those used in other methods (Table 2).

Table 2. Synthesis of Alkyl Benzoates by Alkylation of Benzoates Anions: Comparison of Recent Methods

Method \ Ester	$C_6H_5CO_2iPr$			$pNO_2-C_6H-CO_2Et$			$C_6H_5-CO_2(CH_2)_4O_2C-C_6H_5$		
Our results	24h	60°C	92%	6h	RT	95%	12h	40°C	86%
$C_6H_5CO_2H$ + Resin $\overset{+}{N}(CH_3)_3\bar{O}H$ + iPrBr in hexane [28]	13h	50°C	60%						
$pNO_2-C_6H_4CO_2H$ + EtOH + $(CH_3)_3SiCl$ in THF [29]				48h	78°C	81%			
$C_6H_5CO_2H/KF$ + $Br(CH_2)_4Br$ in DMF [30]							0.5h	130°C	85%
$C_6H_5CO_2K$ + $Br(CH_2)_4Br$ in DMF [30]							1h	140°C	80%

Table 3. Synthesis of Pyrididine Carboxylic Esters by Alkylation of Carboxylates Anions [31]

Alklating agent (catalyst 10%) \ Ester									
Et_2SO_4 (NBu_4Br)	24h	RT	51%	24h	RT	24%	24h	RT	29%
$EtBr(NBu_4Br)$	48	RT	32%	43h	RT	81%	43	RT	93%
$PhCH_2Cl(NBu_4Br)$	20h	RT	68%	24h	RT	81%	24h	RT	74%
$nC_8H_{17}Br$(Aliquat)	24h	85°C	100%	48h	60°C	93%	24h	60°C	93%
$nC_{16}H_{33}Br$(Aliquat)	72h	60°C	90%	72h	60°C	90%	72h	60°C	96%

A problem of selectivity arises with alkylation of pyridine-carboxylates owing to the competitive quaternization of the pyridine ring. Nevertheless, good yields of esters were obtained when a suitable leaving group was selected for the alkylating electrophile (Table 3). As previously observed, Aliquat 336 is the best catalyst for $nC_8H_{17}Br$ and $nC_{16}H_{33}Br$, while nBu_4Br is more efficient for Et_2SO_4, EtBr and $PhCH_2Br$.

II. ETHER SYNTHESIS

(a) Aliphatic Ethers [32]

The best general method for ether synthesis is still the alkoxides alkylation (Williamson reaction) [33].

$$RO^-M^+ + R'-X \rightarrow ROR' + MX$$

Three possibilities of an access of disymetric ROR' ethers were investigated, and are described below.

Method A. Alkylation by $nC_8H_{17}Br$ performed with alkoxides, technical or prepared in aqueous or methanolic solution (MeONa, MeOK, EtONa, tBuOK):

$$\underset{\text{solid}}{MeOK} + \underset{\text{liquid}}{nC_8H_{17}Br} \xrightarrow[2h\ 20°C]{\text{Aliquat } 27\%} \underset{\text{liquid } 76\%}{nC_8H_{17}OMe} + \underset{\text{liquid } 24\%}{C_8H_{16}} + KBr$$

Method B. Alkylation of *in situ* generated alkoxides performed with $nC_8H_{17}Br$:

$$\underset{\text{liquid}}{MeOH} + \underset{\text{solid}}{KOH} + \underset{\text{liquid}}{nC_8H_{17}Br} \xrightarrow[2h\ 20°C]{\text{Aliquat } 2\%} \underset{88\%}{nC_8H_{17}OMe} + \underset{12\%}{C_8H_{16}} + KBr$$

[MeO K]

Method C. Alkylation of *in situ* generated $nOct\bar{O}K^+$ performed with MeI.

$$\underset{\text{liquid}}{nC_8H_{17}OH} + \underset{\text{solid}}{KOH} + \underset{\text{liquid}}{CH_3I} \xrightarrow[2h\ 20°C]{\text{Aliquat } 2\%} \underset{100\%}{nC_8H_{17}OMe} + KI$$

[$nC_8H_{17}OK$]

Evidently, the last method is the best one, as no competitive elimination (octene formation) takes place with MeI as alkylating agent.

Results obtained for $nC_8H_{17}OMe$ synthesis by means of other recently described methods are also indicated in Table 4.

It is apparent that the use of KOH/Aliquat without solvent is the best method; not only is it very easy to perform and inexpensive, but the yield is quantitive within 2 h at room temperature. It also avoids the use of heavy cations such as Hg or Tl (highly toxic), or expensive aprotic solvents, and takes place under very mild and efficient conditions.

Table 4. Recent Methods for Synthesis of $nC_8H_{17}OCH_3$ ($nC_8H_{17}OH$ + base + ICH_3)

Base	Solvent	Time (h)	Temp.	Yield
KOH/Aliquat 2% [32] (our results)	no solvent	24	RT	100%
KF/Alumina [34]	CH_3CN	40	RT	90%
NaOH/NBu_4I 2% [35]	C_6H_6	4	45°C	90%
TlOEt [36]	C_6H_6	14	RT	26%
KOH [37]	DMSO	0.5	RT	83%

It is possible to prepare aliphatic disymetric ethers without solvent, by reaction of generated alkoxides (ROH + K OH) *in situ*, in the presence of a PTC catalyst. Thus, the reaction of $nC_8H_{17}Br$ with an excess of KOH under this condition at 100°C for 7 h, leads to 57% yield of dioctyl ether.

$$nC_8H_{17}Br \xrightarrow{OH^-} nC_8H_{17}OH \xrightarrow{OH^-} nC_8H_{17}O^- \longrightarrow (nC_8H_{17})_2O$$

This result is comparable to the classical liquid–liquid PTC reaction using aqueous NaOH and benzene at 80°C for 4 h, resulting in 75% yield. We performed the reaction $nC_8H_{17}OH$ + KOH + nOctBr in the presence of 2% Aliquat 336 for 2 h at room temperature, obtaining 98% of the isolated ether $(nC_8H_{17})_2O$. These conditions are milder and more efficient than those described in the classical PTC reaction which utilizes aqueous NaOH and benzene, and results in 75% yield after 8 h at 70°C.

A Peculiar Case: t-BuOK

t-BuOK, a strong base, generally leads to large amounts of elimination products. However, in the reaction to t-BuOK with $nC_8H_{17}Br$, using different PTC catalysts and Aliquat 336, no elimination occurred. The last compound was shown to be the most effective.

As in E_2 and SN_2 type reactions, the effect of temperature and catalyst on the elimination is limited. On the other hand, the effect of the leaving group is considerable, as observed in homogenous reactions. Thus, β-elimination is favoured when iodide is a leaving group whereas SN_2 type reaction is favoured when tosylate is a leaving group.

(b) Aromatic Ethers [31, 70]

Aryl ethers are also obtained in high yields (Table 5) without solvent under solid–liquid PTC conditions. In this reaction, phenoxide anions are formed *in situ* with solid KOH, and then alkylated with alkyl halides in "one pot" reaction.

In this case, the yields and the reaction conditions compare favourably with previously described methods (Table 6).

It is significant that long chain halides can also be used with very good results.

III. SYNTHESIS OF ALKYL CYANIDES

Cyanide alkylation is presently under investigation. From preliminary results, it appears that alkyl cyanides can be very easily prepared under mild conditions, *but only in the presence of 1 eq. of water.* Thus KCN reacts (8 h, 20°C) with 1 eq. $Br(CH_2)_5Br$ in presence of 2% Ali-

Table 5. Synthesis of Aromatic Esters [32]

$$ArOH + KOH + RX \xrightarrow{2\%\ Aliquat} ArOR$$

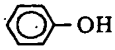
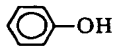
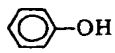
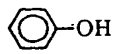
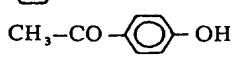
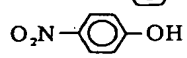
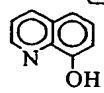
ArOH	RX	Time (h)	Temp.	Yield
	CH_3I	5	RT	99%
	$nC_8H_{17}Br$	2	85°C	98%
	$nC_{16}H_{33}Br$	6	85°C	92%
	nC_4H_9Br	2	60°C	100%
	$nC_8H_{17}Br$	2	85°C	97%
	CH_3I	2	85°C	97%
	$nC_8H_{17}Br$	2	85°C	97%

Table 6. Synthesis of Phenylbutyl Ether: Comparison of Recent Methods (PhO^- + nC_4H_9Br)

Method	Solvent	Time (h)	Temp.	Yield
Our results [31]	no solvent	2	60°C	100%
Liquid–liquid CTP [40]	CH_2Cl_2	12	RT	85%
Gas-liquid CTP [41]	no solvent		170°c (p: 10 Torr)	68%
Triphase catalysis [42]	toluene	2	110°C	99%
Triphase catalysis [43]	toluene	72	100°C	71%
Triphase catalysis [44]	toluene	12	110°C	60%
PhO^- exchanged resin [45]		6	50°C	100%

quat and 1 eq. H_2O to give quantitatively the dinitrile. No reaction takes place in the absence of water. This preparation of $NC(CH_2)_5CN$ is obviously more efficient than those previously described, for instance, classical solid–liquid PTC (3 h, toluene reflux, 70%) [46], or KCN impregnated on alumina reaction (48 h, 85°C, 71% [7b]. Similarly, the reaction of KCN with $PhCH_2Br$ gives, in the presence of 1 eq. H_2O and 2% Aliquat. 99% yield of $PhCH_2CN$ (2 h, 20°C) [71].

IV. SYNTHESIS OF ALKYL FLUORIDES AND RELATED COMPOUNDS

Classical PTC methods lead to an increase in the anionic reactivity of fluoride. However, the "activated" fluoride anion behaves both as a nucleophile and a base, resulting in a competition between substitution, elimination and hydrolysis. These methods necessitate severe experimental conditions [1–4].

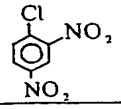
M. Tordeux and C. Wakselman very recently described [47] the preparation of aryl fluorides and fluoroformates using solid–liquid PTC conditions without solvent, and with $(C_2H_5)_3\overset{+}{N}CH_2PhBr^-$ as a catalyst. Under these conditions calcinated KF reacts very poorly with cylchlorides or chromoformates. However, the efficiency of the reaction is considerably increased when KF absorbs H_2O in ~1% of its weight. The effect of a small amount of water on reactivity of fluoride was also observed by S. Dermiek and Y. Sasson [48] who described fluoride anion alkylation in solid–liquid PTC without solvent. Under these conditions, KF in presence of catalytic amount of NBu_4Br and 0.5 eq. H_2O reacted (120°C, 6h) with $nC_8H_{17}Cl$ and gave 93% of $nC_8H_{17}F$. Their results also clearly demonstrate that the catalyst decomposition due to the basic reactivity of the fluoride anion intervenes in the direct fluorination.

We have also performed fluoride alkylation under related conditions [31]. KF appeared quite unreactive at the temperatures we used ($T < 85$°C). However, after addition of 1 eq. of water, the yield of alkyl fluoride increased. Although elimination reaction and the formation of ethers also occurred under these conditions, the latter were formed from fluoride mediated alkylation of the alcohol formed by hydrolysis of the halide.

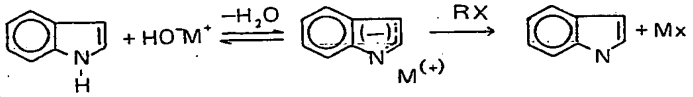
Nevertheless, we were able to obtain high yields of alkyl fluorides and related compounds when working under our usual conditions with CsF or $NBu_4F, 3H_2O$ as the source of fluoride anion (Table 7). The reactions with ethyl bromoacetate and with 2-4-nitrochlorobenzene are noteworthy. The yields and the reaction conditions compare favourably with those described previously, but the use of CsF or $NBu_4F, 3H_2O$ is certainly a limiting factor for this method.

Table 7. Reactions of Fluoride Anion

$$F^-M^+ + RX \xrightarrow{\text{Aliquat } 10\%} R-F$$

F^-M^+	RX	Time (h)	Temp.	Yield
CsF	$PhCH_2Br$	3	85°C	98%
CsF	$nC_8H_{17}Br$	40	85°C	77%
CsF	$nC_{16}H_{33}Br$	65	85°C	80%
CsF	$BrCH_2CO_2Et$	6	40°C	80%
$NBu_4F, 3H_2O$		2	20°C	45%

V. INDOLE ALKYLATION



$M^+ = Na^+, K^+, NR_4^+$ $\quad RX = EtI, Et_2SO_4, nOct\text{-}Br$

Indole alkylation requires the formation of the anion. This was easily done by mixing and stirring, for 5 min, indole with 2.5 eq. KOH (finely ground) and 1% NBu_4Br, and then adding 1.1 eq. of the alkylating electrophile (halide or sulfate). The effect of the quaternary ammonium salt is two-fold: (1) it induces the strong NBu_4OH, and thereby the anion; (2) it increases the nucleophilicity of the indole anion which is associated with the large $\overset{+}{N}Bu_4$ cation. Thus, with solid–liquid PTC, without solvent, N-alkylated indole derivatives are obtained quantitatively under very mild conditions. Better yields are obtained using KOH rather than NaOH as solid base (Table 8).

VI. ALKYLATION OF MALONATE ANION

In 1978, M. Makosza et al. described [49] an efficient alkylation of malonate and other anions using solid–liquid two-phase systems in the absence of solvent. They used anhydrous $KrCO_7$ or Na_2CO_3 to deprotonate the conjugate acids of the nucleophilic anion crown ether, or NBu_4Br or NEt_4Br as catalyst. The reactions were performed at 90–150°C for 1–5 h.

Using tBuOK as the base and Aliquat or NBu_4Br (1–10%) as the catalyst, we prepared [31] (Table 9)

Table 8. N-alkylation of Indole

$$\text{Indole} + KOH + RX \xrightarrow{NBu_4Br\ 1\%} \text{N-alkylindole}$$

RX	Time (min)	Temp.	Yield
$(C_2H_5)_2SO_4$	10	RT	99%
C_2H_5I	10	RT	95%
$nC_8H_{17}Br$	120	50°C	98%

Table 9. Synthesis of Monoalkyl Malonates

$$CH_2(CO_2Et)_2 + tBuOK + RX \xrightarrow{NR'_4X} R-CH(CO_2Et)_2$$

RX	NR'_4X	Time (h)	Temp.	Yield
C_2H_5Br	NBu_4Br 3%	24	RT	96%
$CH_3CH(CH_3)Br$	NBu_4Br 3%	48	RT	100%
nC_4H_9Br	NBu_4Br 3%	24	RT	87%
	Aliquat 3%	24	RT	85%
$nC_8H_{17}Br$	NBu_4Br 3%	30	RT	84%
	Aliquat 3%	30	RT	80%
$nC_{16}H_{33}Br$	Aliquat 10%	30	RT	98%
	NBu_4Br 10%	30	RT	80%

monoalkyl malonates (ethyl, isopropyl, n-butyl, benzyl, n-octyl and n-cetyl) by solid–liquid PTC without solvent. The reactions take place at room temperature and excellent yields are obtained after 1–30 h, depending on the halide. The selectivity is good and with a ratio monoalkylated products: dialkylated products >16, which compares favourably with results previously obtained. It is noteworthy that Aliquat is the most effective catalyst when long chain halide ($C_{18}H_{33}Br$) was used.

VII. β-ELIMINATIONS [72]

We have extended solid–liquid PTC without solvent to base-induced β-eliminations. Secondary halide dehydrogenations are well known in solution [50] or under classical PTC conditions. 2-Bromoctane was studied as a typical weak halide which may undergo either Saitzeff or Hofmann type elimination.

Aliquat appears to be the most efficient catalyst (quasiquantitative β-elimination is observed at room temperature) but the direction of elimination (1-octene/2-octenes) is only slightly affected by the nature of the ammonium salt. On the other hand, direction of elimination is strongly dependent on the nature of the base; the 1-octene/2-octenes ratios increases in the sequence $tBuO^- > OH^- > EtO^- > MeO^-$.

We observed that *tBuOk indicated eliminations* are quantative after 20 h at room temperature *in the absence of any ammonium salt,* but they can be catalyzed by 2% Aliquat (reaction completion within 2 h). With any other bases, no reaction takes place for 20 h at room temperature unless 2% Aliquat is added, resulting in yields >92%. Regioselectivity of elimination at room temperature under our conditions are very close to those obtained when the reactions are performed at reflux in alcoholic media. Our results, using tBuOK, are very similar to those obtained in the tBuOH solution [51a], but are very different to the results in DMSO [51b] or when classical PTC reactions were used [1–4].

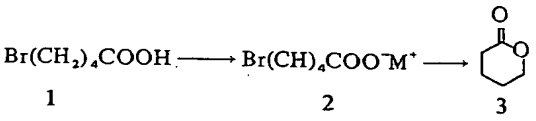
On Table 10 some of our results are indicated as well as those obtained from experiments performed in solvents under PTC and related conditions.

Table 10. Recent Methods for Dehydrohalogenation of 2-Bromooctane

Basic reactants	Time (h)	Temp.	Yield
KF + phosphonium salts [52]	76	102°C	64%
KF + crown-ether (C_6H_6) [53]	($t_{1/2}$=240h)	90°C	68%
polymer supported F^- [54]	30	36°C	73%
tBuOK + crown ether [55] (petroleum ether)	3	60°C	76%
NaOH + NBu_4Br (H_2O–C_6H_6) [56]	48	80°C	86%
KOH/crown-ether (C_6H_6) [57a]	18	80°C	80%
KOH + PEG 600 (C_6H_6) [57a,b]	2	80°C	82%
KOH + PEG 600 + crown-ether (C_6H_6) [56b]	2	80°C	100%
KOH + Aliquat 2% [50]	20	RT	93%
tBuOK without catalyst [50]	20	RT	94%
tBuOK + Aliquat 2% [50]	2	RT	92%
MeOK + Aliquat 2% [50]	20	RT	95%
EtONa + Aliquat 2% [50]	20	RT	92%

VIII. EXAMPLES OF ALKYLATIONS

(a) Intramolecular Alkylation: Synthesis of δ-Valerolactone [73]



5-Bromopentanoic acid is added to 1 eq. of finely ground base NaOme, tBuOK or K_2CO_3 in the presence of 2% Aliquat or in its absence. After 2 h at 40°C, δ-valerolactone is isolated after addition of diethyl ether to the reaction mixture, and filtration on Florisil. Among the bases, K_2CO_3 was found to be the best one; the stronger bases promoted ring opening of δ-valerolactone. In the absence of Aliquat, 81% yield was obtained, but in its presence, the yield increased to 98%. Under these conditions, no intermolecular reactions were observed which could lead to polylactones.

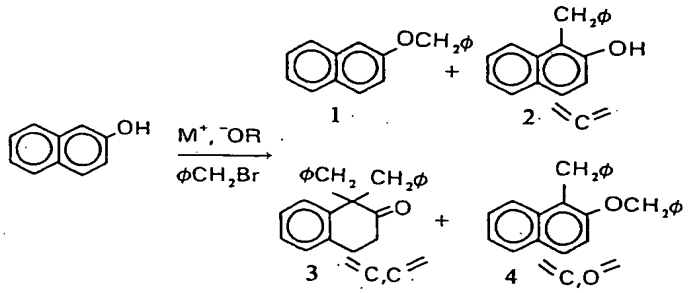
These yields are similar to those obtained by classical homogeneous cyclizations carried out under high dilution with cesium salt in DME [58] or with pyridine thiol ester in C_6H_6 at reflux [59].

This method appears to be complementary to the one of Y. Kimura and S.L. Regen described very recently [60] and in which potassium salt of ω-bromoacid is cyclized in toluene at 90°C in the presence of catalytic amounts of tetralkyl ammonium salts. In our hands, this procedure gave rise to only 27% of δ-valerolactone. On the other hand, Kimura and Regen procedure is superior to ours for 7 member lactone (92% yield vs 30% under our experimental conditions).

Nevertheless, the possibility to mimic high dilution conditions by simple adsorption of a reagent on a reactive mineral support is noteworthy, and may have some theoretical and practical consequences.

(b) Alkylation of β-Naphtoxide Anion [74]

β-Naphtoxide anion is a typical phenolic ambident anion [61c]; its alkylation with $PhCH_2Br$ may lead to four products:



It has been known since the pioneering experiments of N. Kornblum [61] that solvent is a very important factor for the orientation effect in this alkylation: O-alkylation is favoured in polar, aprotic solvents, while C-alkylation in protic solvents. Under liquid–liquid PTC conditions, some O-alkylation was observed [62] but alkylation on alumina in "dry media" [7b,c] led to significant C-alkylations. However, no efficient selective

Table 11: Alkylation of β-Naphtoxyde Anion

a	Base	Time (h)	Temp.	1 "O"	2 "C"	3 "C,C"	4 "C,O"
1:1:1	KOH–Aliquat (40%)	3	60°C	85[b] (75)[c]			7[b]
1:2:2	LiOH	2	85°C		96[b] (87)[c]		
1:3:3	LiOtBu	2	85°C			88[b] (80)[c]	10[b]
1:1:5:1	2 + KOH–Aliquat (40%)	2	85°C			12[b]	85[b] (74)[c]

a. Ratio naphtol/base/$PhCH_2Br$. b. Yield by VPC. c. Yield in isolated product.

method for formation at different alkylated products exists.

We were able to perform four very selective reactions, each leading almost exclusively to only one of the four possible alkylation products (Table 11). All reactions are performed without solvent; O-alkylation are Aliquat catalyzed solid–liquid PTC reactions, KOH being anion-generating base. C-alkylated products are prepared in the absence of ammonium salt, but with LiOH or tBuOLi as the base. When the latter base is used, di-C-alkylated β-naphtol is formed, whereas LiOH results in the mono-C-alkylated product. These results are important not only because of their excellent selectivity, but also because they are performed (1 h, at 85°C), without solvent and catalysis.

PTC Processes Conducted in the Absence of Organic Solvent

(a) Liquid–Liquid PTC. Many examples may be found in the literature [63,64] about liquid–liquid PTC reactions performed without the presence of solvent. Generally, the neat electrophile, sometimes present in excess, constitutes the organic phase [65]. it was observed that the presence of an organic solvent produced a considerable decrease in the reaction rate. Recently, Y. Sasson and H.A. Zahalka [66] have studied the catalyst poisoning effect in liquid–liquid PTC alkylation of aqueous HCO_2Na by alkyl chlorides, and found that this poisoning effect is minimized when highly concentrated formate solutions are used. The presence of an aqueous phase appears to have no advantage with regard to solid–liquid PTC processes.

(b) Gas-Liquid PTC. Gas–liquid PTC reactions were recently described by P. Tundo et al. [24,67a]. These reactions are performed at high temperatures and pressures at which electrophile is in gaseous phase, and the catalyst in a liquid one. This new technique, which is performed under continuous flow conditions, could be of practical interest, for example, in the Wittig reaction.

The Role of Water

Several groups [47,68] have pointed out the importance of small amounts of water in solid–liquid PTC reactions. This effect of water is also important in solid–liquid PTC without solvent reactions, such as in fluoride and cyanide displacements. Water weakens the ionic interactions in the cyrstal, resulting in easier cation exchange with the catalyst and giving rise to nucleophilic anionic species associated with an ammonium cation. The lattice energies for CH_3CO_2K (686 kJ mol^{-1}) and CNK (669 kJ mol^{-1}) [69] are similar, but the former reacts more efficiently, under our conditions, in the absence of water. It is possible that the formation of a local aqueous phase [68] saturated with the nucleophilic salt which is in equilibrium with the solid phase involved, in which case the reaction would take place in the liquid–liquid interface. However, this would not explain the specificity of KCN compared with CH_3CO_2K. On the other hand, the solubilities of the potassium salts in water and of the ammonium salts in the halides may play an important role.

In this account, we wanted to point out that solid–liquid PTC without solvent reactions have several important advantages over the reactions performed in the presence of solvents. They proceed efficiently under milder conditions, very often at room temperature; their work-up is simple and easy. In the case of competitive reactions, a selectivity is often observed.

Acknowledgment. The results we report here are part of a collaborative work. The valuable contributions of Dr. J. Barry, Dr. G. Decodts, Mr. A. Petit, Mr. P. Pigeon and Mr. F. Vaziri-Zand are acknowledged.

REFERENCES

1. W.P. Weber and G.W. Gokel, *Phase Transfer Catlysis in Organic Synthesis*, Springer-Verlag, 1977.
2. C.M. Starks and C. Liotta, *Phase Transfer Catalysis*, Academic Press, 1978.
3. E.V. Dehmlov and S.S. Dehmlov, *Phase Transfer Catalysis*, 2nd edition, Verlag Chemie, 1983.
4. P. Caubère, *Le transfert de phase et son utilisation en chimie organique*, Masson, 1982.
5. E. Keinan and Y. Mazur, *J. Am. Chem. Soc.*, 99, 3861 (1977).
6. a. E. Zadok, C. Aronovitch and Y. Mazur, *Nouv. J. Chim.*, 6, 695 (1982). b. Z. Cohen, E. Keinan, Y. Mazur and T.H. Varkony, *Org. Synth.*, 59, 176 (1980). c. T.C. Jempty, K.A.Z. Gogins, Y. Mazur and L.L. Miller, *J. Org. Chem.*, 46, 4545 (1981).
7. a. G. Bram and T. Fillebeen-Khan, *J. Chem. Soc., Chem. Commun.*, 522 (1979). b. G. Bram, T. Fillebeen-Khan and N. Geraghty, *Synth. Commun.*, 279 (1980). c. G. Bram, N. Geraghty, G. Nee and J. Seyden-Penne, *J. Chem. Soc., Chem. Commun.*, 325 (1980).
8. G. Bram, E. d'Incan and A. Loupy, *J. Chem. Soc., Chem. Commun.*, 1066 (1981); *Nouv. J. Chim.*, 6, 573 (1982).
9. G. Bram and G. Decodts, *Tetrahedron Lett.*, 21, 5011 (1980).
10. J. Barry, G. Bram, G. decodts, A. Loupy, P. Pigeon and J. Sansoulet, *Tetrahedron Lett.*, 23, 5407 (1982); *Tetrahedron*, 39, 2673 (1983).
11. C.M. Starks, *J. Am. Chem. Soc.*, 193, 195 (1971).
12. A.W. Herriot and D. Picker, *J. Am. Chem. Soc.*, 97, 2345 (1975).

13. A. Jonczyk, H. Ludwikov and M. Makosza, *Angew. Chem., Int. Ed. Engl.*, 17, 62 (1978).
14. M. Hedayatullah, *Synth. Commun.*, 12, 565 (1982).
15. M. Makosza and E. Bialecka, *Synth. Commun.*, 12, 565 (1982).
16. H.E. Hennis, J.P. Easterly Jr, L.R. Collins and L.R. Thomson, *Ind. Eng. Chem. Prod. Dev. Res.*, 6, 193 (1967); H.E. Hennis, L.R. Thomson and J.P. Long, *Ind. Eng. Chem. Prod. Dev. Res.*, 7, 96 (1968).
17. R.L. Merker and M.J. Scott, *J. Org. Chem.*, 26, 5180 (1961).
18. R.H. Mills, M.W. Farrar and O.J. Weinkauff, *Chem. Ind. (London)*, 2144 (1962).
19. R.W. Kay, Brit. Patent 916,772 (1963); *Chem. Abstr.*, 59, 2728 (1963). Brit. Patent 966,266 (1964); *Chem. Abstr.*, 60, 10629 (1964).
20. T. Ando, T. Kawate, J. Yamawaki and T. Hanafusa, *Chem. Lett.*, 935 (1982).
21. S. Quici and S.L. Regen, *J. Org. Chem.*, 44, 3436 (1979).
22. C.L. Liotta, H.P. Harris, M. McDermott, T. Gonzales and K. Smith, *Tetrahedron Lett.*, 2417 (1974).
23. H. Normant, T. Cuvigny and p. Savignac, *Synthesis*, 805 (1975).
24. E. Angeletti, P. Tundo and P. Venturello, *J. Chem. Soc., Perkin Trans. 1*, 993 (1982).
25. R.A. Sawicki, *Tetrahedron Lett.*, 23, 2249 (1982).
26. Y. Sasson and H.A. Zahalka, personal communication to A. Loupy, Jerusalem, October, 1983.
27. J. Barry, G. Bram, G. Decodts, A. Loupy, C. Orange, A. Petit and J. Sansoulet, *Synthesis*, 40 (1985).
28. L. Cainelli and F. Manescalchi, *Synthesis*, 723 (1975).
29. M.A. Brook and T.H. Chan, *Synthesis*, 201 (1983).
30. J.H. Clark and J.M. Miller, *J. Am. Chem. Soc.*, 99, 498 (1977).
31. Unpublished results.
32. J. Barry, G. Bram, G. Decodts, A. Loupy, P. Pigeon and J. Sansoulet, *Tetrahedron*, 40, 2945 (1984).
33. J. March, *Advanced Organic Chemistry*, 2nd ed., McGraw-Hill, 1977, p. 357.
34. Y. Yamawaki and T. Ando, *Chem. Lett.*, 533 (1980); 755 (1979).
35. A. Merz, *Angew. Chem., Int. Ed. Engl.*, 12, 846 (1973).
36. H.O. Kalinowski, D. Seebach and G. Crass, *Angew. Chem., Int. Ed. Engl.*, 14, 762 (1975).
37. R.A.W. Johnstone and M.E. Rose, *Tetrahedron*, 35, 2169 (1979).
38. M. Leboeuf, A. Cave and R. Goutarel, *Bull. Soc. Chim. Fr.*, 2100 (1967); A. Loupy, *Bull. Soc. Chim. Fr.*, 2662 (1975).
39. J. Zavada and M. Pankova, *Coll. Czech. Chem. Commun.*, 43, 1080 (1978) and cited references.
40. A. Mc Killop, J.C. Fiaud and R.P. Hug, *Tetrahedron*, 30, 1379 (1974).
41. E. Angeletti, P. Tundo and P. Venturello, *J. Chem. Soc., Perkin Trans. 1*, 1137 (1982).
42. J.G. Hefferman and D.C. Sherrington, *Tetrahedron Lett.*, 1661 (1983).
43. Y. Hamada, N. Kato, Y. Kakamu and T. Shioiri, *Chem. Pharm. Bull.*, 29, 2246 (1981).
44. S.L. Regen and L. Dulak, *J. Am. Chem. Soc.*, 99, 623 (1977).
45. G. Gelbard and S. Colonna, *Synthesis*, 113 (1977).
46. N. Sugimoto, T. Fujita, N. Shigematsu and A. Ayada, *Chem. Pharm. Bull.*, 10, 427 (1962).
47. M. Tordeux and C. Wakselman, *Synth. Commun.*, 12, 513 (1982).
48. S. Dermiek and Y. Sasson, *J. Fluorine Chem.*, 22, 431 (1983).
49. M. Fedorynski, K. Wojciechowski, Z. Matacz and M. Makosza, *J. Org. Chem.*, 43, 4682 (1978).
50. J. Barry, G. Bram, G. Decodts, A. Loupy, P. Pigeon and J. Sansoulet, *J. Org. Chem*, 49, 1138 (1984).
51. a. R.A. Bartsch and J.F. Bunnet, *J. Am. Chem. Soc.*, 91, 1376 (1969); b. *J. Am. Chem. Soc.*, 91, 1382 (1969).
52. D. Landini, F. Montanari and F. Rolla, *Synthesis*, 428 (1974).
53. C.L. Liotta and H.P. Harris, *J. Am. Chem. Soc.*, 96, 9250 (1974).
54. C. Cainelli and F. Manescalchi, *Synthesis*, 472 (1976).
55. E.V. Dehmlov and M. Lissel, *Synthesis*, 373 (1979); *Liebigs Ann. Chem.*, 1 (1980).
56. A.W. Herriot and D. Picker, *Tetrahedron Lett.*, 4521 (1972).
57. a. Y. Kimura and S.L. Regen, *J. Org. Chem.*, 47, 2493 (1982); b. *J. Org. Chem.*, 48, 195 (1983).
58. E.J. Corey and K.C. Nikolaou, *J. Am. Chem. Soc.*, 96, 5614 (1974).
59. W.H. Kruizinga and W.H. Kellog, *J. Am. Chem. Soc.*, 103, 5183 (1981).
60. Y. Kimura and S.L. Regen, *J. Org. Chem.*, 48, 1533 (1983).
61. a. N. Kornblum, R.A. Smiley, R.K. Blackwood and D.C. Iffland, *J. Am. Chem. Soc.*, 77, 6269 (1955). b. N. Kornblum, P.J. Berrigan and W.J. Le Noble, *J. Am. Chem. Soc.*, 85, 1141 (1963). c. N. Kornblum, R. Seltzer and P. Haberfiel, *J. Am. Chem. Soc.*, 85, 1148 (1963).
62. E. d'Incan and P. Viout, *Tetrahedron*, 31, 159 (1975).
63. Ref. 1, p. 13.
64. Some other examples: N. Sugimoto, T. Fujita, N. Shigematsu and A. Ayada, *Chem. Pharm. Bull.*, 20, 427 (1962); M. Cinquini, F. Montanari and P. Tundo, *J. Chem. Soc., Chem. Commun.*, 393 (1975); W.P. Reeves and M.R. White, *Synth. Commun.*, 6, 193 (1976); H.A. Zahalka and Y. Sasson, *J. Mol. Catal.*, 18, 57 (1983).
65. V. Bochi, G. Casnati, A. Dossena and F. Villani, *Synthesis*, 414 (1976).
66. Y. Sasson and H.A. Zahalka, *J. Chem. Soc., Chem. Commun.*, 1347 (1983).
67. a. E. Angeletti, P. Tundo and P. Venturello, *J. Org. Chem.*, 48, 4106 (1983) and cited references; b. *J. Chem. Soc., Chem. Commun.*, 269 (1983).
68. Ref. 1, p. 14 and p. 97.
69. *CRC Handbook of Chemistry and Physics*, 59th ed., CRC Press, Cleveland, pp. D.88–D. 108.
70. G. Bram, A. Loupy, J. Sansoulet and H. Strelecka, *Synth. Commun.*, 14, 889 (1984).
71. G. Bram, A. Loupy and M. Pédoussant, *Bull. Soc. Chim.*, in press.
72. J. Barry, G. Bram, G. Decodts, A. Loupy, P. Pigeon and J. Sansoulet, *J. Org. Chem.*, 49, 1138 (1984).
73. A. Loupy and F. Vaziri-Zaud, *Org. Prep. Proced. Int.*, 16, 292 (1984).
74. G. Bram, A. Loupy, J. Sansoulet and F. Vaziri-Zaud, *Tetrahedron Lett.*, 25, 5035 (1984).

Tetrahedron Letters,Vol.23,No.51,pp 5407-5408,1982 0040-4039/82/515407-02$03.00/0
Printed in Great Britain

EASY AND EFFICIENT ANION ALKYLATIONS IN SOLID-LIQUID PTC CONDITIONS

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Abstract : *Alkylation of anionic nucleophiles such as potassium acetate or potassium indole can be achieved in good yields without solvent either in the presence of NBu_4Br and small amounts of TiO_2 or in the presence of Aliquat 336 ($Oct_3MeN^+Cl^-$).*

We describe here a new method for alkylating organic anions, which requires neither solvent nor solid support, and works in very mild conditions and with a very easy work-up. Two examples are selected which concern anions which either are stable (e.g. CH_3COO^-) or must be obtained from their conjugated acid (e.g. the anion from indole).

ALKYLATIONS OF THE ACETATE ANION

The synthesis of esters by alkylation of carboxylate anions is usually performed using the silver or mercuric salt in a protic or ether solvent or, more recently, the sodium or potassium salt in dipolar aprotic solvents (1). Carboxylate alkylations can also be carried out using phase transfer catalysis (PTC) (2) ; however, formation of n-octyl acetate from CH_3COO^- and n-OctX requires temperatures higher than 80°C.

Very recently, alternative methods have been proposed :

i) use of reagents impregnated on mineral solid supports (3),

ii) gas-liquid PTC, at a temperature ca 150°C and under reduced pressure (20 Torr) (4),

iii) use of polyethyleneglycols immobilized on Al_2O_3 or SiO_2 as PTC catalyst (5).

Our new methods are simpler :

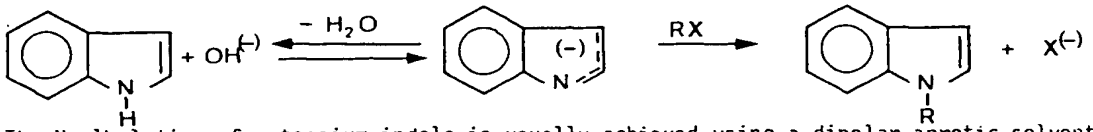
Method I : The reaction was carried out by simply mixing finely ground CH_3COOK with pure n-octyl bromide in the presence of 1 % NBu_4Br and small amounts of TiO_2 (TiO_2 : acetate = 0.2 w/w) (6). After stirring for 5 minutes, the mixture was heated at 60°C for 2 hours to afford n-octyl acetate in 93 % yield. This easy alkylation must certainly imply both an anionic activation of CH_3COO^- by NBu_4Br and an activation of n-OctBr by electrophilic assistance by TiO_2, resulting in a weakening of the C-Br bond.

Method II : By using Aliquat 336 (essentially $Oct_3MeN^+Cl^-$) as the PTC catalyst, n-octyl acetate was obtained in 98 % yield (20 h - room temperature) even in the absence of TiO_2. Very good yields (> 93 %) in benzyl, allyl, n-butyl and cetyl acetates were observed in similar conditions.

The reaction products were easily recovered by simple filtration after addition of

ether. They were qualitatively and quantitatively analyzed by VPC (internal standard) and characterized by IR and NMR.

ALKYLATION OF POTASSIUM INDOLE



The N-alkylation of potassium indole is usually achieved using a dipolar aprotic solvent (DMSO, HMPA) (7) or PTC conditions (8).

To potassium indole prepared by stirring indole with 2.5 mole.eq of ground KOH for 5 minutes in the presence of 1 % NBu_4Br, was then added the pure alkylating agent (e.g. EtI or Et_2SO_4) and the mixture was stirred for 10 minutes at room temperature. After addition of ether and filtration, N-ethyl indole was isolated in 98 % yield. The less reactive n-octyl bromide also reacted smoothly (2 h - 50°C) to give N-octyl indole (yield : 98 %).

Addition of an organic solvent or mineral solid supports did not improve the yield and even proved, in some cases, to be prejudicial to the reaction (9) : for example excess TiO_2 (TiO_2 : acetate = 4), Al_2O_3 or SiO_2 inhibit the alkylation of CH_3COOK by n-OcBr ; Al_2O_3 prevents N-alkylation of potassium indole by Et-I.

The procedures described here, in particular the one using Aliquat 336, are more efficient, less expensive and milder than those published previously, which require more lengthy procedures (3), higher temperatures (3-5) or low pressure conditions (4). We sincerely thank Dr J. SEYDEN-PENNE for very fruitful discussions.

REFERENCES

(1) E. HASLAM, Tetrahedron, 36, 2409 (1980).
(2) W.P. WEBER and G.W. GOKEL, Phase Transfer Catalysis in Organic Synthesis, Springer Verlag, Berlin (1977), pp. 85-95.
(3) G. BRAM, T. FILLEBEEN-KHAN and N. GERAGHTY, Synthetic Comm., 10, 279 (1980).
(4) E. ANGELETTI, P. TUNDO and P. VENTURELLO, J.C.S., Perkin I, 993 (1982).
(5) R.A. SAWICKI, Tetrahedron Lett., 23, 2249 (1982).
(6) In all cases, ammonium salts must be added for the reaction to take place. In the absence of any mineral oxide, the yield was only 73 %. Among all the tested solids (Al_2O_3, SiO_2, ZrO_2, ZnO, MgO, etc...), TiO_2 appeared as the more efficient.
(7) H. HEANEY and S.V. LEY, J.C.S., Perkin I, 499 (1973).
G.M. RUBOTTOM and J.C. CHABALA, Org. Synth., 54, 60 (1974).
(8) A. JONCZYK and M. MAKOSZA, Roczniki Chem., 49, 1203 (1975).
E. SANTANIELLO and C. FARACHI, Synthesis, 617 (1979).
(9) J. BARRY, G. BRAM, G. DECODTS, A. LOUPY, P. PIGEON and J. SANSOULET, to be published.

(Received in France 23 September 1982)

Phase-Transfer Catalysis Communications

Choosing a Phase-Transfer Catalyst for the First Experiment

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Summary: The purpose of the first experiment of a screening program for a new PTC application is to determine if the reaction produces product. Therefore, maximizing reactivity should usually be the focus of the first experiment. Unless data are available to suggest the use of a specific catalyst, it is suggested to choose a catalyst for the first experiment, which is likely to induce reactivity in the widest range of reactions. The catalysts which are most likely to induce reactivity in most PTC categories are Aliquat 336® and tetrabutyl ammonium hydrogen sulfate.

Everyone wants their process improvement or new process development project to show early success. If you are producing organic chemicals, there is a good chance that phase-transfer catalysis, "PTC," will help you achieve high process performance. **Which catalyst do you choose, when you first start evaluating a new PTC application? Why do you choose that catalyst?** That first choice of catalyst can make a big difference.

Unless a specific literature reference is available recommending a specific catalyst for a specific PTC reaction, chemists may just choose for the *first experiment* whatever is "on the shelf," usually tetrabutyl ammonium bromide (TBAB) or tetrabutyl ammonium hydrogen sulfate ($TBAHSO_4$), sometimes Aliquat 336® ($MeN[C_{(8,10)}H_{(17,21)}]_3$ Cl) or triethyl benzyl ammonium chloride (TEBAC). Choosing a convenient catalyst off the shelf for the first screening experiment is often a reasonable thing to do, *if* that catalyst is a good "all purpose" catalyst and it allows you to try the idea while it is still fresh.

Criteria for an All-Purpose PTC "Shelf Catalyst" for Screening

When you start a lab evaluation of a new PTC idea (screening stage), you want to maximize the probability of reaching a firm conclusion, and hopefully, a promising result in the first few experiments. During this early stage screening, the goal is to find out if PTC will work at all for the candidate reaction. The goal is *not* to discover a fully optimized process, product purification scheme, lowest cost catalyst, etc. during the first

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experiment. The key observation sought, especially during the first experiment, is appearance of product. Therefore, in the first experiment we usually try to stack the deck in favor of maximizing **reactivity**.

Background for Discussing "Screening Catalysts"

A review of thousands of PTC publications and patents consistently reveals that chemists usually choose from among a handful of phase-transfer catalysts for screening. These include TBAB, $TBAHSO_4$, Aliquat 336® and TEBAC. TBAB is by far the most highly reported catalyst. In fact, a surprising number of publications as well as patents, report the use of TBAB and never provide an example of any other catalyst. This is especially surprising for patents, for which the driving force of economic feasibility should dictate attempting to identify the "optimal" catalyst. A screening program using just one catalyst may be acceptable if the goal of the project is just to "make some" product. However, if the goal is to obtain the product in high yield in the lab/plant or to achieve a short cycle time in the plant, more than one catalyst should be screened before publication or patent filing. Since in a surprisingly large number of cases, the first catalyst tried is the only one ever reported (usually TBAB), then it is particularly important to choose the best catalyst for *screening*.

Sometimes polyethylene glycols, other ammonium salts (e.g., tetrahexyl ammonium bromide), phosphonium salts (e.g., hexadecyl tributyl phosphonium bromide) and crown ethers are screened during the first few experiments. These are good catalysts and are appropriate for comprehensive screening programs. In fact, more catalysts should be added to this list such as methyltributyl ammonium chloride and selected polypodands. However, time management pressures often dictate very limited screening programs and $TBAB/HSO_4$, Aliquat 336® and TEBAC are overwhelmingly screened. One of the driving forces for writing this article is having observed projects being dropped after only one experiment which provided negligible or 0% conversion. [This is especially frustrating and applicable to projects in which the first experiment used the popular TEBAC catalyst]. Therefore, the purpose of this article is to present an underlying thought process and supporting data for choosing a phase-transfer catalyst which should be kept on the shelf of every organic chemist for use in first experiments. The catalyst chosen for screening new applications should be readily available and have the highest likelihood of inducing reasonably *high reactivity in the broadest range of organic reactions.*

Please note that this article does not suggest that a single phase-transfer catalyst will meet all of the criteria for commercial development. Each PTC application is unique and will require a proper determination of the optimal catalyst. There are many commercial PTC applications which are best performed with each of the catalysts discussed and others. This article focuses on the first experiment only because in every project, a first experiment is inevitable and a choice of catalyst must be made.

Catalyst Factors Which Affect Reactivity

When considering common quaternary ammonium salts as phase-transfer catalysts, there are five major catalyst structure factors which affect reactivity in the PTC application: (1) organophilicity, (2) accessibility of the positive charge of the nitrogen, (3) counteranion, (4) stability and (5) interfacial tension (sometimes). The ultimate choice of catalyst for the final commercial PTC process will take into account other factors such as catalyst separation, catalyst cost, catalyst availability, toxicity, and solubility in waste streams. If a single phase-transfer catalyst was commercially available which was better than most other commercially available phase-transfer catalysts, in *all reactivity attributes*, then it would be an excellent candidate for screening in the first experiment. If the catalyst also meets the other process criteria such as cost, separation and likelihood of contaminating an aqueous waste stream, then it would indeed be a very good commercial phase-transfer catalyst. The following discussion will show that Aliquat 336® and $TBAHSO_4$ are probably the best catalysts for screening new PTC applications for reactivity. TEBAC is *sometimes* an excellent catalyst for reactivity, but it is *not* "universal." TEBAC is totally ineffective in several major reaction categories. Aliquat 336® and $TBAHSO_4$ almost always work.

Reactivity and Mechanism

Several mechanisms are usually at work during PTC reactions, but usually a combination of two processes dominates the rate behavior.[1] These processes are (1) the intrinsic reaction, usually occurring in the organic phase and (2) transfer, usually of anion from a aqueous or solid phase to an organic phase. Reactions in which the reaction rates are limited by the intrinsic reaction are termed "I-reactions." Reactions in which the reaction rates are limited by transfer are termed "T-reactions."

The rate determining step of an I-reaction is the attack of a nucleophile, base, oxidizing agent or other anion

[1] Starks, C.; "Phase-Transfer Catalysis: Mechanism and Syntheses, ACS Symposium Series 659," Halpern, M. ed., American Chemical Society, Washington DC, 1997, Chapter 2

associated with the quat on the substrate. Under certain reaction conditions, the rate expression of I-reactions can simply be:

$$\text{rate} = k_{chem}[QX]_{org}[\text{substrate}]_{org}$$

where k_{chem} is the rate constant of the chemical reaction and $[QX]_{org}$ is the concentration of the ion pair between the quat and the desired reacting anion, X^-, in the organic phase in which the reaction takes place. According to this rate expression, the structure of the catalyst can affect the rate of such I-reactions in four major ways:

(1) being *organophilic* enough to solubilize the reacting anion, X^-, in the organic phase, thereby increasing $[QX]_{org}$
(2) being introduced with a *less polarizable counteranion* which does not strongly associate with the quat, thereby providing less competition to X^- for extraction into the organic reaction phase and increasing $[QX]_{org}$
(3) being *stable* enough under the reaction conditions to continue to be active and extract X^- into the organic reaction phase, thereby increasing $[QX]_{org}$
(4) forming a *loose ion pair* with X^- thereby enhancing its reactivity by increasing k_{chem}

The most common quats used for screening in the literature are TBAB/HSO_4, Aliquat 336® and TEBAC and are compared based on their attributes for I-reactions in Table 1.

(1) For I-reactions, quats are considered organophilic from about 16 carbons and are effective up to about 32 carbons. Below 16 carbons, quats often induce no reactivity (see for example, the S_N2 reaction of thiophenol with octyl bromide[2] or the isomerization of allylbenzene[3]). Above 32 carbons, the quats become less effective due to difficulty in extracting anions from the aqueous or solid phase resulting from their large footprint at the interface (low concentration) and the shielding of the positive charge.[1] Aliquat 336® has approximately 25 carbons and most salts of this catalyst are nearly totally soluble in common organic solvents. Tetrabutyl ammonium (TBA) salts generally distribute between the aqueous and organic phases. If, for example, a TBA salt is 2/3 distributed into the organic phase and the corresponding methyltricaprylyl ammonium salt is totally soluble in the organic phase, then the $[QX]_{org}$ term will be affected accordingly. TEBA salts are often not very soluble in organic solvents. Even TEBA salts of anions which are usually easily extracted into chlorinated hydrocarbons (e.g., MnO_4^-)[4] are not nearly as soluble as the TBA salts. When using even less polar solvents, the differences in $[QX]_{org}$ can be quite dramatic. For example, in toluene (more common in modern commercial applications which prefer to avoid chlorinated hydrocarbons), the solubility of $MeNOct_3$ MnO_4 is 0.8M while TBA MnO_4 is only 0.00034M.[5]

Table 1: Catalyst Structure Comparison for I-Reactions

	TBAB/HSO_4	Aliquat 336®	TEBAC
organophilicity	16 carbons	~25 carbons	13 carbons
counteranion	Br/HSO_4	Cl	Cl
stability	med	med-hi	low
loose ion pair	q = 1	q = 1.4	q = 1.6

(2) Usually, introducing the quat with a less polarizable counteranion is desirable. Chloride is usually preferred over bromide, since the relative extractability of monoanions (X^-) is 3-50 times higher in the presence of chloride relative to bromide.[6] Aliquat 336® and TEBAC contain chloride compared to the bromide of TBAB. TBA chloride may be a good catalyst, but is not readily available commercially (it is made from the bromide). $TBAHSO_4$ is usually advantageous over the chloride and bromide and indeed this catalyst is often a good screening catalyst (it is much more expensive than the other three common catalysts but is readily available).

The extractability of dianions is sometimes enhanced by diquat ion pairs.[7] The ion pairs between dianions and common quats show interesting behavior (Table 2).

In some cases, the bromide and even the iodide can actually induce higher reactivity than the chloride. This occurs when the organic substrate can be activated by converting it to a bromide which may be more reactive.

[2] Herriott, A.; Picker, D.; J. Amer. Chem. Soc., 1975, 97, 2345

[3] Halpern, M.; Sasson, Y.; Rabinovitz, M.; J. Org. Chem., 1983, *48*, 1022

[4] Herriott, A.; Picker, D.; Tetrahedron Lett., 1974, 1511

[5] cited in Starks, C.; Liotta, C.; Halpern, M.; "Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives," 1994, Chapman and Hall, New York p. 502

[6] see ref 5, pp. 27, 31 and 35 based on references cited therein

[7] Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M.; Tetrahedron Lett., 1989, 1683

Table 2: Extractability of Selected Dianions

quat salt	$Cr_2O_7^{-2}$	$Fe(CN)_6^{-3}$	phthalate
$Oct_3NMe^+ Cl^-$	0.56	0.32	0.17
TBA HSO_4	0.59	<0.03	0.08
TBAB	0.47	0.04	0.05
TEBAC	0.01	0.02	not reported

For example, an alkyl chloride alkylating agent can be converted to an alkyl bromide alkylating agent by the attack of the bromide introduced with the quat. *This happens more often than is probably realized by academic and commercial PTC development teams.*

Nevertheless, the chloride counteranion usually induces higher reactivity than bromide. This is especially true when there are no leaving groups such as bromide or tosylate. Thus, ClO^- oxidations,[8] isomerizations[3] and deuterations are usually much more active with the counteranions: $HSO_4^- > Cl^- > Br^-$.

In addition, S_N2 reactions, such alkylation, cyanation, azide preparation, etc. will liberate a bromide or chloride leaving group. After significant reaction occurs (for example 50 mole%), the catalyst counteranion (present at only 1-5 mole%) will be "outnumbered" by the leaving group anion and the catalyst counteranion will no longer significantly affect the reaction rate. Thus, in such cases, the reaction rate is mostly affected by the catalyst counteranion at the outset of the reaction. So as not to minimize the importance of the beginning of the reaction, it should be remembered that the economics of a chemical process depend significantly on the process cycle time (reactor hours) and any improvement (i.e., reduction) in cycle time translates into profit.

(3) Stability studies showed that Aliquat 336® is approximately 70% more stable than TBA chloride, approximately 2.5 times more stable than benzyl trihexyl ammonium chloride and 4-5 times more stable than TEBAC in the presence of 50% NaOH at 25°C.[9]

(4) The looseness of the ion pair is related to the accessibility of the positive charge on the nitrogen atom of the quat. An empirical parameter, "q," which may represent accessibility was suggested[10] and is calculated by adding the reciprocals of the number of carbons on each chain of the quat. If this parameter is representative of accessibility of the positive charge then a lower q value should result in a looser ion pair and should induce higher reactivity. TBA should then induce higher reactivity than Aliquat 336® which in turn should induce higher reactivity than TEBA.

When taking into account the catalyst structure effects discussed above which influence the rate of I-reactions, it may be concluded that Aliquat 336® is more likely to give higher reactivity than TBAB, though both would work. $TBAHSO_4$ will usually work better than TBAB. TEBAC is rarely an acceptable catalyst for I-reactions. Since we usually do not know for sure before the first experiment if the candidate reaction will be an I-reaction or a T-reaction, then we should eliminate TEBAC from the "short list" of catalysts to be screened for the first experiment of a totally new PTC project.

Following are examples PTC reactions believed to be I-reactions. Comparisons of catalysts are highlighted when available.

Example Reactions - Esterification

Esterification is one of the most highly patented reactions using PTC. The classical PTC patent of all time by Starks reports the quantitative esterification of acetate in example 6.[11] Aliquat 336® was chosen as the catalyst for this reaction as well as for 20 other examples of nucleophilic substitutions and oxidations.

Esterifications are usually performed without the addition of solvent since the starting materials and/or products are usually liquid and their structures (such as alkyl halides) are appropriate to serve as effective "solvents" for PTC.

When reporting on the comparison of Aliquat 336® with TBAB for acetate esterifications (see Table 3), Bram et al[12] wrote: "Aliquat 336® is far superior to NBu_4Br for acetate alkylation performed with nC_4H_9Br, $nC_8H_{17}Br$ and $nC_{16}H_{33}Br$; alkyl acetates are thus obtained with yields >92% at room temperature." The difference in reactivity disappears for highly reactive alkylating agents such as benzyl bromide.

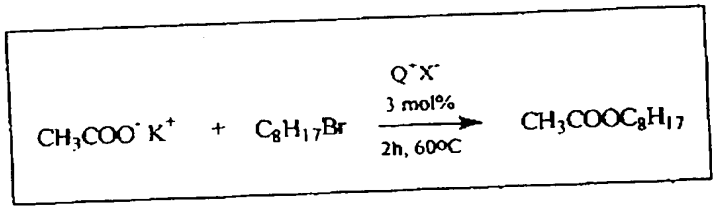
Aliquat 336® and $TBAHSO_4$ were screened for transesterification of methyl esters (see Table 4).[13] The

[8] Lee, G.; Freedman, H.; (Dow Chemical). 1978, US Patent 4,079,075
[9] Landini, D.; Maia, A.; Rampoldi, A.; J. Org. Chem., 1986, *51*, 3187
[10] ref 5, p. 281
[11] Napier, D.; Starks, C.; (Continental Oil) US Patent 3,992,432 (1976)
[12] Bram, G.; Loupy, A.; Sansoulet, J.; Isr. J. Chem., 1985, *26*, 291
[13] Barry, J.; Bram, G.; Petit, A.; Tetrahedron Lett., 1988, 4567

reason for the reversal of the effect of catalyst on the yields of these two esterifications is not clear.

In the polyesterification reaction between bisphenol-A and the diacid chloride ClCOPhC$(CH_3)_2$PhCOCl, the order of reactivity and inherent viscosity increase was Aliquat 336® > TBAB >> TEBAC (see Table 5).[14]

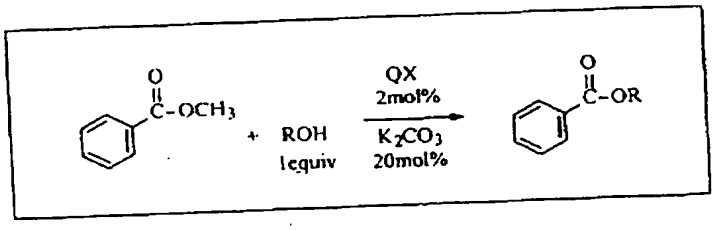
Table 3: Effect of Catalyst on Esterification



	2h/60°C	20h/r.t.	20h/r.t./10mol%
Aliquat 336®	98%	68%	98%
TBAB	73%	2%	not reported
TEBAC		not reported	

Reaction conditions: 11 mmol CH_3COOK, 10 mmol OctBr, 3mol% QX unless stated otherwise, time and temp as shown; no water, no added solvent

Table 4: Effect of Catalyst on Transesterification



ROH	time/temp	Aliquat 336®	$TBAHSO_4$
2-ethylhexan-1-ol	55°C/3h	99%	10%
2-octanol	70°C/10h	13%	72%

Example Reactions - O-Alkylation (Etherification)

The first PTC O-alkylations published were landmark publications for synthesis (typically 90-100% yield) and reported one catalyst each (TBAB,[15] benzyl tributyl ammonium chloride[16] and TBA iodide[17]). More recently, the extraction of phenol from a simulated waste stream (5000 ppm) and reaction with allyl bromide showed that the more organophilic catalysts

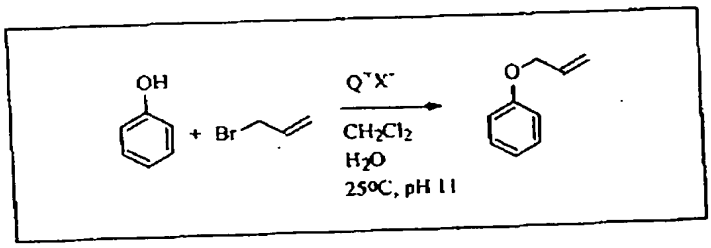
Table 5: Effect of Catalyst on Polyesterification

	Yield	η (dl/g)
Aliquat 336®	90%	0.50
TBAB	81%	0.17
TEBAC	48%	0.11

Reaction conditions: 2.5mmol bisphenol-A, 5mol% catalyst, 25 mL 0.3M NaOH; 20 mL water, 20 mL CH_2Cl_2, 2.625 mmol diacid, 5 mL CH_2Cl_2, 20°C, 60 min

gave higher rates of phenol consumption.[18] In this case it would appear that organophilicity is more important than counteranion. It is interesting that tetrabutyl *phosphonium* bromide gave a rate of 5.25 M/min, which is nearly double that of TBAB. Phosphonium salts are more lipophilic than ammonium salts.

Table 6: Effect of Catalyst on O-Alkylation[18]



catalyst	rate (M/min)
Aliquat 336®	6.37
$TBAHSO_4$	3.45
TBA Br	2.29
TEBA Cl	0.163

Reaction conditions: 50mL aqueous phase containing 5000 ppm phenol at pH 11; 83 mmol allyl bromide, 0.62 mmol QX, 50 mL CH_2Cl_2; 25°C

Bram et al compared several PTC and non-PTC etherification systems (for example, the reaction of n-octanol with methyl iodide) and reported "It is apparent that the use of KOH/Aliquat without solvent is the best method; not only is it very easy to perform and inexpensive, but the yield is quantitative within 2 h at room temperature."[12]

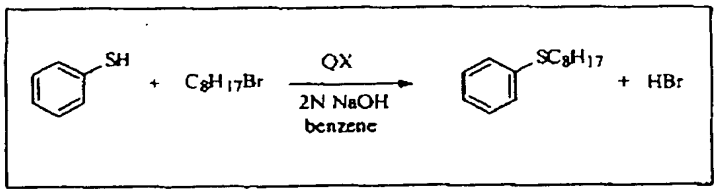
Example Reactions - S-Alkylation

The first publication to report a comprehensive screening of catalysts for any PTC reaction was for the alkylation of thiophenol (see Table 7).[2] The paper is one of the classic PTC publications. Aliquat 336® outperformed 19 other catalysts except for two

[14] Tagle, L.; Diaz, F.; Campbell, W.; Eur. Polym. J., 1993, *29*, 1069
[15] Freedman, H.; DuBois, R.; Tetrahedron Lett., 1975, 3251
[16] McKillop, A.; Fiaud, J.; Hug, R.; Tetrahedron, 1974, *30*, 1379
[17] Merz, A.; Angew. Chem. Int. Ed. Eng., 1973, *12*, 846
[18] Wu, H.; Lai, J.; Ind. Eng. Chem. Res., 1995, *34*, 1536

phosphonium salts and a crown ether which gave rate constants 20-30% higher.

Table 7: Effect of Catalyst on S-Alkylation



catalyst	k_{obs} x 1000 1/Msec
Bu_4P Br	37
Aliquat 336®	31
TBAB	5.2
Pr_4N Br	0.0056
TEBA Br	< 0.0016

Reaction conditions: 2.0115g OctBr, 3.0171g PhSH, 1.0047g $C_{14}H_{29}$, 40 mL PhH, 0.00137 mol catalyst, 50mL 2N NaOH, 30°C

Example Reactions - Oxidation

H_2O_2 can be transferred into organic solvents by incorporation into the "hydration" shell of a quat-anion pair. The transfer of H_2O_2 into CH_2Cl_2 by quat salts is shown in Table 8.[19]

Table 8: Effect of Catalyst on H_2O_2 Transfer

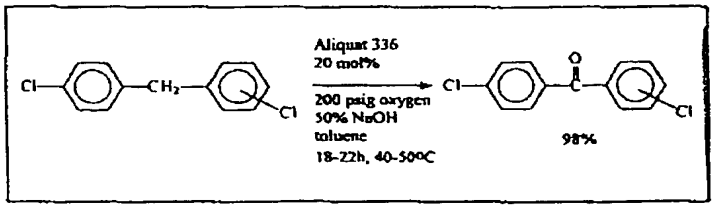
quat salt	equiv H_2O_2 transferred / equiv quat salt
Oct_4N Br	1.00
Aliquat 336®	0.88
TBA Br	0.68
TBA Cl	0.3
$TBAHSO_4$	0.1
TEBA Cl	0.013

Aliquat 336® appears to be the best commercially available quat for hydrogen peroxide transfer. In fact, hydrogen peroxide epoxidations are performed using Aliquat 336®.[20,21] They usually require the addition of tungstate/phosphate to stabilize the peroxide.

The first hypochlorite oxidations were reported using $TBAHSO_4$ as the catalyst.[8]

Activated hydrocarbons can be oxidized by deprotonation with concentrated NaOH and reaction with oxygen.[22] Aliquat 336® and $TBAHSO_4$ again were the best commercially available catalysts (see Table 9). The maximum conversion resulted from a combination of organophilicity, counteranion and stability factors.

Table 9: Effect of Catalyst on Base-Promoted Oxidation



quat salt	maximum conversion
Aliquat 336®	98%
Oct_4N Br	93%
TBA HSO_4	90%
TBA Br	67%
TEBA Cl	44%

Example Reactions - Hydrolysis

The saponification of diethyl adipate showed great sensitivity to both counteranion and quat structure (see Table 10).[23] The effect of counteranion in this case is the greatest since hydroxide transfer is difficult (affecting $[QOH]_{org}$) though not rate determining. Catalyst decomposition would not be a significant factor in this reaction which was performed at room temperature. These results cause one to wonder how effective would be Aliquat 336® if it had an HSO_4 counteranion.

Table 10: Effect of Catalyst on Hydrolysis

catalyst	yield
$TBAHSO_4$	93%
Aliquat 336®	50%
TBA Cl	32%
TBA Br	18%
TEBA Cl	18%

Reaction conditions: 10 mmol diethyl adipate, 50 mmol 50% NaOH, 5mL pet ether, 0.2mol% catalyst, 1h, r.t.

[19] ref 5, p. 522 and reference cited therein
[20] Au, A.; (Dow Chemical) **1991** US Patent 5,036,154
[21] Venturello, C.; Alneri, E.; Lana, G.; **1981** Ger. Offen. 3,027,349
[22] Halpern, M.; Lysenko, Z.; J. Org. Chem., **1989**, *54*, 1201
[23] Dehmlow, E.; Barahona-Naranjo, S.; J. Chem. Res. (S), **1979**, 238

Example Reactions - Dehydrohalogenation

The mechanism of PTC dehydrohalogenations has been the subject of debate and firm conclusions have not been widely accepted. Therefore, it is difficult to predict the effect of catalyst. Empirically, several interesting observations have been made regarding the effect of catalyst. Early dehydrobrominations were performed with $TBAHSO_4$. The use of $TBAHSO_4$ in dehydrobrominations sometimes requires the use of stoichiometric amounts of quat.[24] Dehydrobromination of 2-phenethylbromide proceeded well catalytically with Oct_4N Br and slowly with TEBA Br.[25] Didehydrobromination to obtain alkynes could be performed catalytically only with highly organophilic quats such as Aliquat 336® and tetraoctylammonium bromide.[26] $TBAHSO_4$ and TEBAC did not didehydrobrominate under catalytic conditions. Dehydrochlorinations proceed well with $TBAHSO_4$.[27] A patent reported the dehydrochlorination of an adduct of dichlorosuccinate.[28] This dehydrochlorination has a strong driving force to conjugate two carbonyl groups. Under comparative conditions, Aliquat 336® gave 78% yield, $MeNBu_3$ Cl gave 56% yield and TEBAC gave 8% yield. TBA Cl was screened in the early stages of the project but was not evaluated under the final set of comparative conditions.

The largest volume dehydrochlorinations are performed using β-hydroxyalkyl quats.[29] Such quats should be screened based on the optimization literature published.[30] However, these are highly specialized quats and may not be appropriate for determining if your candidate dehydrohalogenation will work during the first experiment. In other work, highly reactive dehydrobromination was observed when a "third phase" could be formed using TBAB.[31] Careful adjustment of temperature and concentration needed to be manipulated to obtain the third phase. The search for a third phase during an optimization stage is a very useful practice because it can lead to great improvements in process profitability, however, it should not be the target of a first experiment. Again, for screening experiments, we want to choose a phase-transfer catalyst which is likely to work catalytically for the widest variety of dehydrohalogenations. The only catalyst which qualifies is Aliquat 336®.

Example Reactions - Transition Metal Co-Catalysis

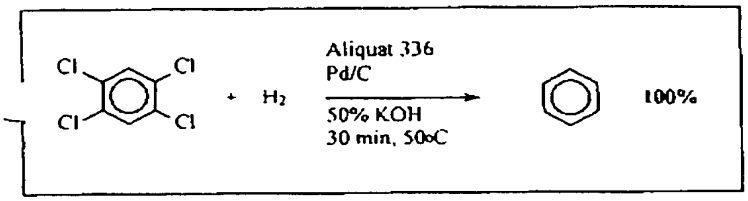
There is little in the literature to suggest which catalyst should be chosen for transition metal co-catalyzed PTC ("PTC/TM") reactions. All three classic quats (Aliquat 336®, TBA, TEBA) appear in the PTC/TM literature. Starks used tridecyl methyl ammonium chloride (Aliquat 336® is a 2:1 mixture of $(C_8:C_{10})_3NMe$ Cl) in most of the PTC/TM oxidations reported in the classic PTC patent.[11] Alper's group performed many PTC/TM reactions,[32] including carbonylations using hydroxide. In the early years, they used primarily TEBAC[33] and more recently they use other catalysts (e.g., Hex_4NHSO_4[34]). Carbonylations have also been performed using Aliquat 336®.[35,36] Sasson's and Blum's groups have coordinated $RhCl_3$ and $PtCl_4$ with Aliquat 336® to make $Q^+RhCl_4^-$ and $Q^+PtCl_5^-$ which are totally soluble in organic solvents and performed subsequent catalytic reactions.[37,38] Recent work on the Heck reaction used $TBAHSO_4$/Br with excellent results.[39] Other work with palladium also used TBA salts.[40,41,42] Three publications actually screened a number of phase-transfer catalysts used with palladium. $PdCl_2(PPh_3)_2$/formate was used in hydrodebromination and showed catalyst effectiveness as follows: Hex_4NHSO_4 > Aliquat 336® > $TBAHSO_4$.[43] In another hydrodebromination, $PdCl_2(PPh_3)_2$/benzyl alcohol was used and Aliquat 336® gave approximately double the maximum rate of reaction relative to TEBAC. TEBAC was slightly faster than Hex_4NBr.[44] Hydrodechlorination with Pd/C and hydrogen showed

[24] Gorgues, A.; Le Coq, A.; Tetrahedron Lett., 1976 4723
[25] Halpern, M.; Ph.D. Thesis, 1983, Hebrew Univ of Jerusalem
[26] Dehmlow, E.; Lissel, M.; Tetrahedron, 1981, 1653
[27] Halpern, M.; Zahalka, H.; Sasson, Y.; Rabinovitz, M.; J. Org. Chem., 1985, *50*, 5088
[28] Maulding, D.; (American Cyanamid) 1989, US Patent 4,847,405
[29] Maurin, L.; (DuPont) 1983, US Patent 4,418,232
[30] Kurginyan, K.; Mendeleev Chem. J. Eng. (Allerton), 1986, *31*, 74
[31] Mason, D.; Magdassi, S.; Sasson, Y.; J. Org. Chem., 1991, *56*, 7229
[32] Alper, H.; Adv. Organomet. Chem., 1981, 183
[33] for example, Alper, H.; des Abbayes, H.; J. Organomet. Chem., 1977, *134*, C11
[34] Amaratunga, S.; Alper, H.; J. Organomet. Chem., 1995, *488*, 25
[35] Younis, K.; Amer, I.; Organometallics, 1994, *13*, 3120
[36] Badrieh, Y.; Blum, J.; Schumann, H.; J. Mol. Catal. 1994, *90*, 231
[37] Sasson, Y.; Zoran, A.; Blum, J.; J. Mol. Catal., 1981, *11*, 293
[38] Baidossi, W.; Schumann, H.; Blum, J.; Tetrahedron, 1996, *52*, 8349
[39] Jeffery, T.; Galland, J.; Tetrahedron Lett., 1994, 4103
[40] Vlassa, M.; Ciocan-Tarta, I.; Margineanu, F.; Oprean, I.; Tetrahedron, 1996, *52*, 1337
[41] Wang, J.; Hu, Y.; Cui, W.; Synth. Commun., 1994, *24*, 3261
[42] Choudary, B.; Reddy, N.; Ashok, B., Applied Catal., 1987, *32*, 357
[43] Bar, R.; Sasson, Y.; Blum, J.; J. Mol. Catal., 1982, *16*, 175
[44] Hallgren, J.; Lucas, G.; J. Organomet. Chem., 1981, *212*, 135

highest reactivity with Aliquat 336®.[45] A large phosphonium salt gave high conversion, but too large of an ammonium salt (60 carbons) decreased activity (see Table 11). $TBAHSO_4$ and TEBA Br were not effective.

Again, since clear guidelines are not available for choosing a catalyst for all PTC/TM reactions, the first experiment of a new PTC/TM screening program should probably be run with Aliquat 336® or possibly Hex_4NHSO_4.

Table 11 : Effect of Catalyst on Hydrodechlorination



catalyst	time (h)	% conversion
Aliquat 336®	0.5	100%
$C_{16}H_{33}PBu_3$ Br	1.5	100%
$C_{16}H_{33}N(C_{18}H_{37})_3$ Br	1.5	63%
TEBA Br	1.5	no reaction
$TBAHSO_4$	2.0	no reaction
PEG-2000	1.5	no reaction

Reactions in Which TEBAC Excels

The discussion and data presented above relate to I-reactions and are not encouraging for TEBAC fans. With so much discouraging TEBAC data (reactivity and stability), how could this catalyst become so popular? The answer is because TEBAC truly is an outstanding catalyst for a great many PTC applications. Since Makosza first published the C-alkylation of phenylacetonitrile in 1965[46] using TEBAC, hundreds of PTC/OH applications have been published, patented and commercialized. Makosza himself used TEBAC in scores of synthetic publications[47] for C-alkylations, N-alkylations, carbene reactions and nucleophilic aromatic substitutions, even before Starks coined the term "phase-transfer catalysis." Some attribute the widespread use of TEBAC as a "shelf catalyst" for screening new PTC applications, to Makosza's prolific publication of TEBAC.[48]

Instead of just using TEBAC to screen PTC/OH reactions, it would be desirable to be able to predict the effect of quat structure on PTC reactions which do not abide by the standard I-reaction criteria. Unfortunately, not enough is understood about non-I-reaction PTC systems to fully characterize them and predict optimal conditions with certainty. The mechanism(s) of PTC/OH reactions have always been the subject of great debate. It is thought that some combination of interfacial and extractive processes govern the course of PTC/OH reactions.[1,49] Conclusive evidence has been provided to show that interfacial tension is an important factor in at least one PTC/OH alkylation.[50] If a PTC reaction were transfer rate limited ("T-Reaction") then reduction of interfacial tension would enhance the reaction rate, regardless if the mechanism were interfacial or extractive. In contrast, since the rate determining step of an I-reaction is in the organic phase, the rate at which the anion crosses the phase boundary would be irrelevant history in determining the overall reactivity of the reaction. Interfacial tension is just one example of an effect of quat structure which would manifest itself quite differently for I-reactions vs T-reactions. It would not be surprising, therefore, to observe radically different reactivity behaviors of PTC systems based on quat structure.

We can use these observations to examine these anomalous PTC/OH systems[51] on an empirical basis. Other than "knowing" that TEBAC seems to work well for certain types of PTC/OH reactions, only a few studies were reported which compare a variety of catalysts. Two of these studies suggest empirical guidelines for THIS[51] category of PTC/OH reactions (the concepts of interfacial tension[50] and accessibility[52] to be discussed below).

[45] Marques, C.; Selva, M.; Tundo, P. *Gazz. Chim. Ital.*, **1996**, *126*, 317

[46] Makosza, M.; Serafinowa, B.; Rocz. Chem., **1965**, *39*, 1223

[47] Makosza, M.; Pure Appl. Chem., **1975**, *43*, 439

[48] I must admit that I used TEBAC exclusively, following historical precedent, when I performed my first undergraduate PTC research in the 1970's. I was lucky that I did not choose to perform I-reactions in that early work or I may have been discouraged by the use of TEBAC and moved into some other field of chemistry for my carecr.

[49] Makosza, M.; "Phase-Transfer Catalysis: Mechanism and Syntheses, ACS Symposium Series 659," Halpern, M. ed., American Chemical Society, Washington DC, **1997**, Chapter 4

[50] Mason, D.; Magdassi, S.; Sasson, Y.; *J. Org. Chem.*, **1990**, *55*, 2714

[51] please note that not all PTC/OH reactions are anomalous; some PTC/OH systems are clearly I-reactions such as the isomerization of allylbenzene (ref 3)

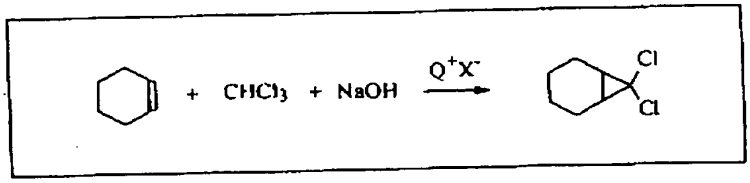
[52] Halpern, M.; Sasson, Y.; Rabinovitz, M.; *Tetrahedron*, **1983**, *38*, 3183 and ref 25

Example Reactions - Carbene Addition

The most comprehensive screening of catalysts for a PTC/OH reaction was reported by Dehmlow and Lissel.[53] The reaction studied was the reaction of cyclohexene with dichlorocarbene and dibromocarbene generated from chloroform and bromoform. They reported the results for 28 ammonium quats and 19 other phase-transfer catalysts. Data are presented for selected quats in Table 12.

TEBAC does seem to perform better than the other chlorides. Polarizable anions seem to reduce the reactivity. The homologous quat bromide series is difficult to interpret. Taking the broader perspective, it is clear that TEBAC is a good catalyst, as opposed to the 1-reaction systems discussed earlier. It is interesting to note that the same study which was performed for the addition of dibromocarbene to cyclohexene showed smaller differences in reactivity between catalysts.

Table 12: Effect of Catalyst on Carbene Addition



catalyst	yield	catalyst	yield
TEBA Cl	51%	Et_4N Br	44%
Aliquat 336®	42%	Pr_4N Br	26%
Bu_4N Cl	39%	Bu_4N Br	29%
Pr_4N Cl	34%	Pnt_4N Br	32%
		Hex_4N Br	35%
Bu_4N HSO_4	46%	Hep_4N Br	28%
Bu_4N Cl	39%	Oct_4N Br	23%
Bu_4N Br	29%		
Bu_4N I	23%		

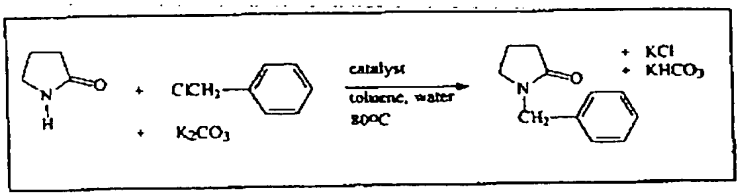
Reaction conditions: 0.1 mol cyclohexene, 0.4 mol $CHCl_3$, 0.2 mol 50% NaOH, 0.001 mol catalyst, 4h, 23°C

Example Reactions - Alkylation

Alkylation reactions usually show clearer trends. The N-benzylation of pyrrolidinone showed that TEBAC outperformed the larger catalysts (Table 13).[54]

In order to truly evaluate the effect of quat structure on a given reaction, it is important to systematically change the structure of the catalyst, including non-symmetrical catalysts. Unfortunately, only one such study was reported (many studies report one homologous series or only symmetrical quats) and that was for the methylation of deoxybenzoin[52] (Table 14).

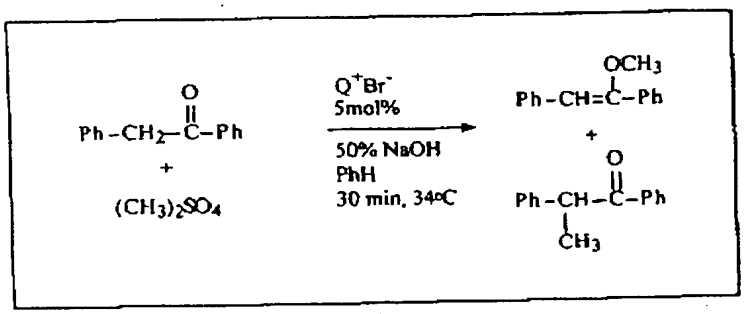
Table 13: Effect of Catalyst on N-Alkylation



catalyst	initial rate (mmol/dm^3 min)
TEBAC	5.00
TBAB	2.49
Hex_4N Cl	1.45

Reaction conditions: 25 mmol 2-pyrrolidinone, 25 mmol benzyl chloride, 50 mmol K_2CO_3, 2.5 mmol QX, 25 mL toluene, 80°C

Table 14: Effect of Catalyst on Alkylation



quat salt		conversion at 30 min	q value
$BuNEt_3$	Br	100%	1.8
TEBA	Br	not measured (expected placement)	
$OctNEt_3$	Br	98%	1.6
$MeNBu_3$	Br	95%	1.8
Et_4N	Br	85%	2.0
$EtNBu_3$	Br	79%	1.3
$MeNOct_3$	**Br**	**67%**	**1.4**
Bu_4N	**Br**	**54%**	**1.0**
$EtNOct_3$	Br	47%	0.9
Pnt_4N	Br	45%	0.8
Hex_4N	Br	40%	0.7
$BuNOct_3$	Br	36%	0.6
Oct_4N	Br	29%	0.5
Me_4N	Br	21%	4.0

[53] Dehmlow, E.; Lissel, M.; Tetrahedron Lett., 1976, 1783
[54] Sasson, Y.; Bilman N.; J. Chem. Soc. Perkin Trans II, 1989, 2029

The qualitative concept of accessibility was proposed based on the observation of these data which show that the presence of even one methyl group or several ethyl groups resulted in higher reactivity (too much accessibility of the positive charge of Me_4N leads to so much hydrophilicity that the catalyst's function degrades significantly). Several years later a simple calculation was proposed to attempt to characterize accessibility: "q" = sum of the reciprocals of the number of carbons of each linear chain of the quat. Before the q value was suggested, it was obvious that alkyltriethyl ammonium quats were somehow structurally fit to catalyze this type of PTC/OH reaction well. The q value provided a means to compare non-symmetrical quats. For example, the q value of $MeNBu_3$ was similar to that of the $RNEt_3$ and gave similar reactivity. The q values of homologous series of $RNBu_3$ and $RNOct_3$ correlated well with the reactivities of these quats. The q value was suggested only as an empirical parameter. Reactivity of certain types of PTC/OH reactions seem to increase as the q value increased up to about 1.5-2 then decrease. **The commercially available quat which has the most carbons (good for I-reactions) and also has the closest q value to 1.5-2.0 (good for this category of PTC/OH reactions) is $MeNOct_3$ (q = 1.4, C# = 25; similar to Aliquat 336®).** The quat with the next highest q value (below 1.5) and the most number of carbons is Bu_4N (q = 1.0, C# = 16).

Back to the Central Question...
Which Catalyst Should I Try First?

The central question which the current article addresses is how to maximize the chances of making the first PTC experiment work. Therefore, it would be desirable to choose a catalyst which induces the highest reactivity possible in *both* categories of I-reaction and T-reaction. This is because *we cannot predict with certainty* if a reaction will be intrinsic reaction rate limited or transfer limited before we run the first experiment. Empirical examination of the PTC systems shown above for both I-reactions as well as T-reactions indicates that Aliquat 336® and TBA HSO_4 induce relatively high reactivity in both categories. In some cases, they may not induce as much reactivity as TEBAC, but they can certainly be chosen to **span the I-reaction and T-reaction categories.**

Despite the sensibility of the approach to focus on reactivity in the first experiment, the temptation still exists to find the "magic bullet" on the first experiment. Some chemists may prefer to screen Aliquat 336® first because it is much less expensive, more readily available and more thermally stable than $TBAHSO_4$. Aliquat 336® also will not be likely to contaminate aqueous waste streams because it is so organic soluble. Some chemists will compromise the reactivity of $TBAHSO_4$ and use TBAB instead, which is more competitive in price with Aliquat 336®. TBAB can often be separated from the product by water washing (which may or may not be desirable). Aliquat 336® is particularly suitable for commercial use when the product is distillable or recrystallizable. However, these considerations are beyond the scope of the discussion to determine which catalyst to use for the first experiment. Let's face it, you do have to choose a catalyst for the *first* experiment. So you might as well make an informed decision. It is recommended that you try either Aliquat 336® or $TBAHSO_4$. Either of these two catalysts will give you the best shot at obtaining some product in the first experiment.

If *neither* Aliquat 336® nor $TBAHSO_4$ show promising results, then there is a decision tree to further evaluate the feasibility of the PTC process. If *either* Aliquat 336® or $TBAHSO_4$ show promising results, then there is a whole other decision tree to further evaluate the feasibility and optimize the PTC process. These decision trees start with the first experiment and are the keys to effective (high process performance) and efficient (short development time) PTC process research.

About the Author - Dr. Marc E. Halpern

Dr. Marc E. Halpern is a leading authority on **increasing profit** for client companies using phase-transfer catalysis (PTC) technology. Dr. Halpern provides consulting and training which focus on all practical, theoretical and organizational aspects to identify opportunities, develop and implement PTC technology in commercial industrial processes. Dr. Halpern helped companies save > **$16 million/yr** in process improvements. In 1995/6, Dr. Halpern provided consulting and training at > **50 industrial sites** in the US, Europe, the Middle East and Asia.

Dr. Halpern authored/co-authored the classic books and training programs "*Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*" (Chapman & Hall, 1994) "*Enhancing Process Profitability Using Phase-Transfer Catalysis*" (PTC Communications, Inc. 1995), "*Practical Phase-Transfer Catalysis*" (PTC Communications, Inc. 1996). Dr. Halpern composed the guidelines for evaluating and optimizing new PTC applications and invented the accessibility parameter for characterizing the effect of phase-transfer catalyst structure on reactivity and selectivity. Dr. Halpern has an impressive track record from Organic Process Chemist to Director, Research and Development over a 12 year period in the chemical industry.

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Day 2 Agenda: Identifying Profit Opportunities; Applications: Strong Base Reactions: C-Alkylation, Chiral Alkylation, O-Alkylation, S-Alkylation, N-Alkylation, Michael Addition, Aldol Condensation, Wittig, Darzens, Dehydrohalogenation, Carbene Reactions; Nucleophilic Substitutions, Esterification, Thiophosphorylation, Cyanide, Azide, Fluoride, other nucleophilic aliphatic and aromatic substitutions; Other Reactions: Oxidations, Reductions, Other PTC reactions, Exercises; Conclusion.

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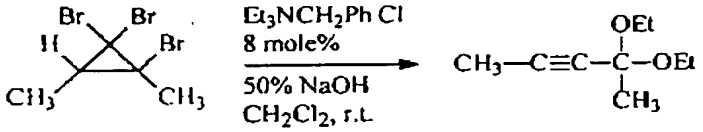
PTC Reactions and Applications

N-Alkylation

Mono-N-alkylation of a nonactivated diamine with a benzyl chloride derivative was performed using 8 mole% Bu_4NI, 18 mole% KI and 100 mole% $KHCO_3$ in THF achieving 72% yield. The catalyst was separated from the product by water extraction. Wilkerson, W.; Rodgers, J. (DuPont Merck Pharmaceuticals) **1996** US Patent 5,508,400

O-Alkylation

Trihalocyclopropanes were formed by the PTC/OH carbene reaction of haloform with haloalkene (Et_3NCH_2Ph Cl as catalyst). The trihalocyclopropane was then reacted with ethanol/NaOH using Et_3NCH_2Ph Cl as catalyst to obtain the diethoxide, ring opening and dehydrohalogenation to afford the acetylenic acetal. Sydnes, L.; Bakstad, E. *Acta Chem. Scand.*, **1996**, *50*, 446



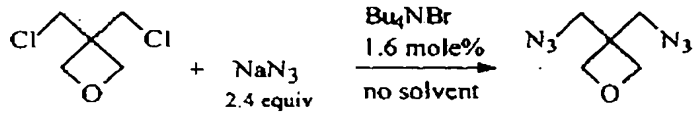
+ EtOH 80%

Cyanide Reactions

The dramatic effect of hydration on PTC cyanide activity is exemplified by a patented discovery by Brown and Rawlinson. They used cyanide in the rearrangement of a keto-enolester to a triketone using Bu_4NBr as the catalyst. When they used 3.7 moles H_2O per mole of enol ester they achieved 81.6% yield. Without added water, no desired product was obtained and using 8 moles H_2O per mole of enol ester, less than 1% product was obtained! Selection of hydration levels provides great opportunities and great pitfalls in PTC process development. Brown, S.; Rawlinson, H. (Zeneca) **1996** WO 96/22958

Azide Reactions

A 50 gallon scale azide/halide substitution was reported in an impressive Aerojet patent by Malik et al. The temperature was controlled by controlling the rate of addition of starting material into the stirred reactor. The catalyst was separated and product purified by a combination of extraction with water and passing the product stream through alumina. The filtered product stream was > 99% pure. I like this patent because it describes a simple, high yield, high purity reaction which is scaleable and provides an apparently safe process integrating the expertise of the inventors with the strengths of PTC.



94%

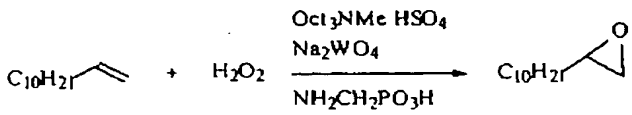
Aliquat 336® was used to perform the S_N2 reaction between azide and taxol derivative with a trifluoromethanesulfonyl leaving group (7-position). The catalyst was separated and product purified by chromatography. Menichincheri, M.; Ceccarelli, W.; Ciomei, M.; Fusar Bassini, D.; Mongelli, N.; Vanotti, E. (Pharmacia) **1996** WO 96/14309

Oxidation

Dibutyl sulfide was oxidized to dibutyl sulfone in 90% isolated yield using 30% H_2O_2, 0.3 mole% Na_2WO_4 co-catalyst, 3 mole% Bu_4NCl, $ClCH_2CH_2Cl$ as solvent at 40°C for 5 h. No H_3PO_4 was used as in previous H_2O_2/WO_4 oxidations. Stec, Z.; Zawadiak, J.; Skibinski, A.; Pastuch, G. *Pol. J. Chem.*, **1996**, *70*, 1121

Epoxidation

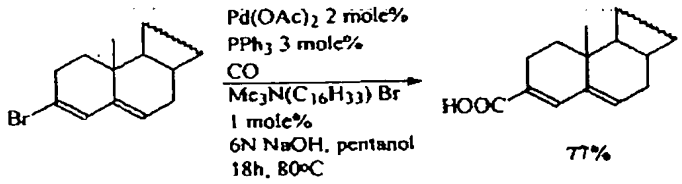
PTC H_2O_2/tungstate epoxidations of olefins have been of significant interest since 1983 and incremental improvements have been reported since. Noyori et al. have developed an environmentally-friendly epoxidation procedure using no halogens and no solvent. 1-Dodecene was epoxidized by 30% H_2O_2 in the presence of Na_2WO_4, α-aminomethylphosphonic acid and methyl trioctyl ammonium hydrogensulfate. After 2 h at 90°C the distilled yield was 87%. If toluene was added as a halogen-free solvent, the yield was 97% after 4 h. This article also provides a good historical perspective and references for the development of PTC/H_2O_2/tungstate epoxidation. Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.*, **1996**, *61*, 8310



87% (97%)

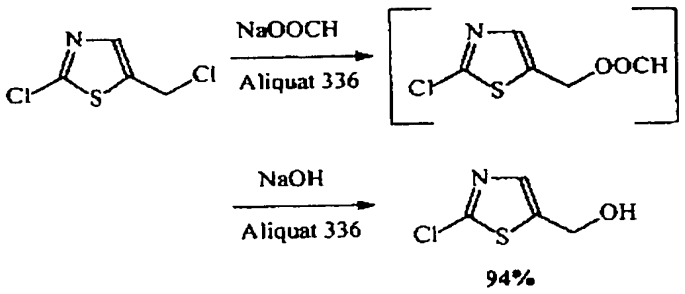
Carbonylation

We are surprised to find few PTC carbonylation patents issued, but here's one. The catalysts were separated by extraction into water and the product purified by recrystallization. Baine, N.; McGuire, M.; Yu, M. (SmithKline Beecham) **1996** WO 96/11206



Hydrolysis

Leanna and Morton applied the combined strength of PTC esterification with the sensitivity of formate esters to hydrolysis to effectively convert an alkyl chloride to the corresponding alcohol. The use of formate for this conversion is an excellent general method for the conversion of RCl to ROH (see Zahalka, H.; Sasson, Y. Synthesis, **1986**, 763) and better than the use of acetate (used in the earlier US Patent 4,387,253). Leanna, R.; Morton, H. (Abbott Laboratories) **1996** WO 96/16050



Bu_4NHSO_4 (5 mole%) was used with 14% NaOH to completely hydrolyze a thiazolidine carboxylate ethyl ester within 30 min. The catalyst was separated by water extraction. Poli, S.; Magni, A.; Bocchiola, G. (Poli Industria Chimica) **1996** WO 96/10036

New Catalysts

The interactions between crown ethers and cations were studied by preparing and comparing the properties of 18-crown-6 with 18-crown-5. The article describes a lot of thermodynamics. Pictures showed why 18-crown-5 binds more than 1000 times weaker than 18-crown-6. Raevsky, O.; Solovev, V.; Solotnov, A.; Schneider, H.; Rudiger, V. *J. Org. Chem.*, **1996**, *61*, 8113

Following are references which describe properties and syntheses of new crown ethers and related compounds:

Synthesis of chiral pyridino-18-crown-6:
Habata, Y.; Bradshaw, J.; Young, J.; Castle, S.; Huszthy, P.; Pyo, T.; Lee, M.; Izatt, R. *J. Org. Chem.*, **1996**, *61*, 8391

Synthesis of benzoazacrowns and benzocryptands using the Mannich reaction:
Pastushok, V.; Bradshaw, J.; Bordunov, A.; Izatt, R. *J. Org. Chem.*, **1996**, *61*, 6888

Thiolariat ether selective for Ag^+:
Nabeshima, T.; Tsukada, N.; Nishijima, K.; Ohshiro, H.; Yano, Y. *J. Org. Chem.*, **1996**, *61*, 4342

Synthesis of bibrachial lariat ether attached to the two nitrogens of 4, 13-diaza-18-crown-6 (2 of the 6 oxygens of 18-crown-6 are replaced by nitrogens):
Katritzky, A.; Belyakov, S.; Sorochinsky, A.; Steel, P.; Schall, O.; Gokel, G. *J. Org. Chem.*, **1996**, *61*, 7585

Upcoming Events

ChemSpec 97

will be held in Manchester, UK, Jun 10-12. On June 11, Marc Halpern will be presenting the talk "Reducing Cost of Manufacture of Organic Chemicals Using PTC."

1997 International PTC Conference

will be held in Nagoya, Japan, Sep 25-27. Contact Professor Shioiri, Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-Dori, Mizuho-ku, Nagoya 467, JAPAN. Tel 81-52-8363439, Fax 81-52-8349309, E-mail: shioiri@phar.nagoya-cu.ac.jp

Organic Process R&D Conference

will be held in San Francisco, Nov 5-7. Marc Halpern will be presenting the talk "Practical PTC: Enhancing Both Reactivity and Catalyst Separation." Contact Scientific Update: Tel 44-1435-873062, Fax 44-1435-872734, E-mail: scientificupdate@dial.pipex.com

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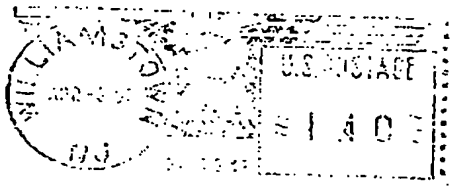

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PTC Course in **ITALY** - *see page 13*